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"The ultimate measure of a man is not where he stands in moments of comfort and convenience but where he stands at times of challenge and controversy."

Ds Marthen Luther King

To the dedicated medical staff of Nyanje R.C.Z. Hospital - Zambia.

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VOORWOORD

Het lijkt op een "blaasontsteking". Continue pijnlijke aandrang tot plassen. Pijn in de blaasstreek, jaren achtereen. Plassen lucht op, de WC wordt dus zeer frequent gezocht en bezocht. Zowel overdag als ’s nachts. Kan dat zo erg zijn dat je de voorkeur geeft aan een stoma boven de eigen blaas? Bij een ’goedaardige’ aandoening? Ja dat kan als de diagnose **cystitis interstitialis (blaas-pijnsyndroom)** luidt.

Dat geeft een machteloos gevoel, zowel voor de patient als de behandelend arts. Het doet mij herinneren aan mijn tropenjaren in Zambia. De wanhopige machteloosheid als een kind overleed, zonder diagnose en zonder dat de behandeling effect had. Wat kon je ook met de beperkte middelen in een ziekenhuis zonder telefoon, zonder stroom, met slechts een stroomgenerator voor ’s avonds, en met twee uur stromend water per dag. In de Westerse wereld kan toch meer? De rijkdom van een Nederlands academisch ziekenhuis vertaalt zich o.a. in een immense bibliotheek waar m.b.v. de CD-ROM de hele wereld-literatuur beschikbaar is. Helpen, behandelen, genezen, maar hoe dan?

Het verwijt aan de hedendaagse gezondheidszorg is dat men vaak door blijft behandelen, ook wanneer men weet dat genezing niet mogelijk is. Bij een aandoening als cystitis interstitialis dreigt precies het omgekeerde: omdat ’genezing’ niet mogelijk is, daalt de animo tot behandelen. De twijfels rond diagnostiek en behandeling hebben daar alles mee te maken. Maar is er eigenlijk wel verschil tussen genezen en behandelen? Kuitert defineert geneeskunde als "mensen helpen te ontkomen aan het kwaad van ziekte, lichamelijke gebreken en dood"[1]. Een ’kunst’ die de Afrikaanse *n’anga* (medicijnman) beter verstaat dan menig westers dokter. Immers, in Afrika heeft elke ziekte zijn ’reden’. In onze westerse cultuur wordt de ’reden’ ingeperkt tot een medische diagnose. Geen diagnose?, dan zal het wel "tussen de oren" zitten. Mede om die reden eindigt een cystitis interstitialis patient niet zelden bij de psychiater of psycholoog[2]!

Al meer dan 80 jaar worden de klachten van cystitis interstitialis patienten gedetailleerd beschreven, zonder dat de medische wetenschap dichter bij de oorzaak of genezing is gekomen. We weten dat 9 van de 10 cystitis interstitialis patienten vrouw is, vaak met een leeftijd tussen 20 en 60 jaar en dat de diagnose vooral gesteld wordt op basis van de typische klachten en slijmvliesafwijkingen van de blaas. Microscopisch onderzoek van blaasbiopten is niet specifiek voor de diagnose. De oorzaak is even onbekend als 80 jaar geleden en een genezend medicijn bestaat (nog) niet. Alleen een urine stoma blijkt effectief te zijn. Een wel heel desastreuze oplossing bij vaak jonge vrouwen. Hoe dan te (be)handelen? Sommige medicijnen geven verlichting zonder dat het

precieze werkingsmechanisme bekend is. Een *placebo-effect*? Een placebo-geneesmiddel bevat geen werkzame chemische bestanddelen en een *placebo-effect* is een verbetering van gezondheidsklachten die volgt op een medische interventie maar die niet medisch verklaard kan worden[3]. Misschien valt veel van wat door medici, alternatieve genezers of de n'anga bereikt wordt onder deze noemer. Maar of het 'genezende kruid' in de vorm van capsule, thee of magische dans wordt toegediend, het zal de patient een zorg zijn als de klachten maar verdwijnen.

De pijn in de blaasstreek, de aandrang en het frequente WC bezoek maken dat elke cystitis interstitialis patient vroeg of laat bij de uroloog komt. Heeft de uroloog meer te bieden dan alternatieve genezers of de n'anga? Meer dan een urine-stoma? Ja! Allereerst kan hij of zij de diagnose stellen. Een belangrijk 'houvast' voor de patient en haar omgeving en de eerste stap om het zelfgenezend vermogen van patienten te mobiliseren[4]. Immers, met eenvoudige 'zelf-help' is het mogelijk de klachten dragelijker te maken. Een patient enkele minuten aanhoren en de ernst van haar klachten bevestigen heeft vaak al een verbluffend effect. Het kan zelfs telefonisch. Het 'mogen bellen' geeft de patient een ruggesteun, versterkt het 'zelf-genezend' vermogen. En dan zijn er een aantal medicijnen. Door objectieve en subjectieve resultaten reproduceerbaar vast te leggen kan de uroloog het specifieke effect van een toegediend medicijn vergelijken met dat van *placebo*. Zo kan, nadrukkelijk samen met de patient, gewerkt worden aan een leefbare situatie, zonder een urinestoma en zo mogelijk klachtenvrij.

De eerder genoemde machteloosheid, de diep gevoelde noodzaak tot werken aan genezing ("helpen te ontkomen aan het kwaad van cystitis interstitialis") en tegelijk de uitdaging om meer te weten te komen van deze aandoening vormden de basis voor dit promotie onderzoek.

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Preface

It resembles cystitis. A continuous painful, urgent desire to pass urine. Cramplike pain in the lower abdomen, year after year. Urinating gives relief; a W.C. is therefore sought and visited frequently. Both day and night. Can it be so awful that you prefer a stoma to your own bladder? To treat a 'benign' condition? Yes, it can if the diagnosis is **interstitial cystitis (the painful bladder syndrome).**

Interstitial cystitis provokes a feeling of powerlessness, for the patient and the treating physician. It reminds me of my years in the tropics, in Zambia. The desperate impotence when a child died, without a diagnosis and without the treatment having any effect. What were you to do with the limited means, in a hospital without a telephone, without electricity, with the generator only on in the evenings and with two hours of running water per day? In western civilisation we have a great deal more to offer. The wealth of a Dutch university hospital translates itself into assets such as an immensely large library, where CD-ROM can be used to access the world literature. Helping, treating, healing. But in this case, HOW?

Modern health care is often reproached because it continues to apply treatment, even when a cure is no longer possible. With a disease such as interstitial cystitis, precisely the opposite threatens to happen: because there is no 'cure', there is little inclination to prescribe treatment. Doubts surrounding diagnosis and treatment are chiefly to blame. But is there really a difference between curing and treating? Kuitert defined medicine as 'helping people to escape the evil of disease, physical disabilities and death'[1]. An 'art' that the African n'anga (medicine man) understands better than many western doctors. In Africa, every disease has a 'reason', while in our western culture the 'reason' is restricted to a medical diagnosis. No diagnosis?, then the problem probably lies 'between the ears'. For reasons such as these, interstitial cystitis patients are often referred to a psychologist or psychiatrist[2].

Detailed descriptions of the symptoms of interstitial cystitis patients have been appearing for more than 80 years, without medical science coming any closer to the cause or cure. We know that nine out of ten interstitial cystitis patients are women, usually aged between 20 and 60 years and that the diagnosis is made largely on the basis of typical symptoms and anomalies of the mucous membrane lining the bladder. We are just as much in the dark about the cause as we were 80 years ago and a medicinal cure is still lacking. Only a urine stoma seems to be effective; a very disastrous solution for the (often young) patients. How should we deal with these patients then? Some medications give relief without us knowing the precise mechanism. A *placebo-effect*? Placebo medication does not contain any active chemical constituents, while a *placebo effect* means medically unexplainable improvement of the symptoms following medical intervention[3]. Perhaps a great deal of what physicians, homoeopaths, or the n'anga

achieve can be placed under this common denominator. The patient will not care at all whether the 'healing potion' is applied in the form of tablets, tea or a magic dance, as long as the symptoms disappear.

Pain in the lower abdomen, urgency and the frequent visits to the W.C. guarantee that sooner or later, every patient with interstitial cystitis will be referred to the urologist. Does the urologist have more to offer than homoeopaths or the n'anga More than a urine stoma? Yes! First of all, he or she can make the diagnosis - give it a name. An important 'foothold' for the patient and her close associates and the first step towards mobilising the self-help potential of the patient[4]. With simple self-help it is possible to make the symptoms more bearable. Just listening to a patient for several minutes and confirming the gravity of her complaints will often make an amazing difference. It can even be done by telephone. 'Being allowed to call' gives the patient support and strengthens her 'self-healing' potential; and there are also a few medications available. By recording objective and subjective results in a reproducible manner, the urologist can evaluate the specific effect of a medication compared to *placebo*. In this way - expressly in a joint effort with the patient - we can work towards a livable situation, without a urine stoma and if possible, symptom-free.

The above-mentioned powerlessness, the deeply felt need to work towards a cure (*helping to overcome the evil of interstitial cystitis*) and at the same time, the challenge to find out more about the disease, formed the basis for this thesis.

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CHAPTER 1

INTRODUCTION AND OUTLINE OF THE THESIS

Interstitial cystitis (IC) is thought to be an uncommon lesion of the urinary bladder which was probably first described by Nitze in 1907 and termed cystitis parenchymatosa[1]. It was popularised by Hunner in 1914, who called it " a rare type of bladder ulcer", and subsequently, the "elusive" ulcer[2]. The term "elusive" was well-chosen; indeed, eight decades later IC remains a mysterious disease engulfed in a shroud of confusion concerning its diagnosis, etiology, pathogenesis and treatment. Hunner's ulcer has become the typical characteristic of 'classic' interstitial cystitis. Although actually not a true ulcer, only a velvety red patch and only present in a small minority of IC patients.

In 1984, IC patients in the U.S.A. founded the ICA (Interstitial Cystitis Association). According to patient's experience the disease was not-appreciated by medical doctors, rather than uncommon. After just one appearance of the ICA president on national television, ABC's "Good Morning America" (1984), the ICA received over 10.000 letters within 2 weeks. It was the start-off of a boom in publicity, funding and IC research in the U.S.A. Over the period 1991 to 1994 IC research funding ranked third in percent increased federal funding (145%), following breast cancer with a 200% increase and ovarian cancer with a 157% increase. Even higher than the increase in AIDS research funding (30%). Despite these overwhelming efforts we are still far from determining a cause for this illnes or syndrome, and we still do not have an effective treatment that provides more than temporary symptomatic relief. A committee convened by the National Institutes of Health (U.S.A.) has arbitrarily proposed a set of characteristics to define the disease[3].

A comprehensive overview of literature and a current view of experts on interstitial cystitis is provided in several recent publications[4 - 8].

It can be expected that with time all interstitial cystitis patients will consult a urologist because of the severity of the complaints. In **Chapter 2** we conducted a survey among all urologists in The Netherlands, to provide the prevalence of IC in The Netherlands and the most common diagnostic and therapeutic approaches by Dutch urologists.

With no pathologic findings specific for interstitial cystitis, diagnosis of the condition can be extremely difficult. It remains essentially a diagnosis of exclusion[9]. Numerous attempts have been made to find abnormalities associated with the symptoms of interstitial cystitis which might serve

as objective diagnostic marker or therapeutic parameter. Tamm-Horsfall protein (THP) has been related to interstitial cystitis. Auto-antibodies against THP and bladder deposits of THP were reported in IC patients[10,11,12]. We attempted to further investigate the role of THP in interstitial cystitis. **Chapter 3** reports on the THP urinary production in interstitial cystitis patients and controls, as well as the presence or absence of THP in bladder tissue biopsies. Implications towards the etiology of interstitial cystitis are discussed.

An auto-immune etiology of interstitial cystitis has been suggested for many years[13]. **Chapter 4** describes a study which was designed to evaluate the presence of tissue-specific auto-antibodies in IC patients using a direct immunostaining technique not reported before in relation with IC patients.

Chapter 5 comprises the first of a series of therapeutical trials, a clinical controlled pilot-study with intravesical pentosanpolysulfate instillations. Afterwards, a placebo-controlled, double-blind, trial with intravesical pentosanpolysulfate was undertaken. The results are discussed in **Chapter 6**. Based on the results of the placebo-controlled study, we aimed to increase the therapeutic efficacy by adding oxybutinin. In **Chapter 7** we report on the study with intravesical pentosanpolysulfate versus the application of pentosanpolysulfate combined with oxybutinin, again in a double-blind setting.

If conservative treatment fails in patients suffering from disabling interstitial cystitis, surgical management is inevitable. A number of surgical alternatives have been proposed. Unfortunately persisting pain, urgency and frequency, similar to the pre-operative symptoms are well-recognised complications[16,17]. In **Chapter 8** our assessment of the most appropriate surgical technique is discussed, based on the analysis of the records of all interstitial cystitis patients treated at our hospital between 1976 and 1991.

Usually dietary manipulation is part of the treatment of interstitial cystitis patients in the U.S.A.[14,15]. Our urologist-based questionnaire, conducted in 1994, revealed that only 34% of Dutch urologists occasionaly use dietary advise in the treatment of interstitial cystitis. In a prospective study, presented in **Chapter 9**, we evaluated the dietary habits of interstitial cystitis patients and compared them to the average diet of the general population. We also investigated whether there was any spontaneous preference or avoidance of specific foodstuffs and fluids by IC patients.
Finally, the results of our studies are summarized in **Chapter 10**.

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CHAPTER 2

INTERSTITIAL CYSTITIS IN THE NETHERLANDS: PREVALENCE, DIAGNOSTIC CRITERIA AND THERAPEUTIC PREFERENCES

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The annual meeting of the Dutch Society for Urology, Veldhoven, The Netherlands, May 1995.

Abstract.

Purpose. To determine the prevalence of interstitial cystitis in The Netherlands and to analyse the most common diagnostic and therapeutic approaches among Dutch urologists.

Materials and Methods. A questionnaire was filled in by urologists and analysed with the help of a statistical computer program.

Results. The prevalence of interstitial cystitis was calculated between 8 to 16 per 100,000 female adults. Pathology of bladder biopsies and mast cells were the main diagnostic criteria. DMSO instillations, bladder hydrodistension and surgery were the most frequent applied therapies.

Conclusions. The prevalence of interstitial cystitis in the Netherlands is in line with other reports from Europe, but low compared to the USA. The importance of pathology and mast cells in diagnosis and less awareness might contribute to this difference.

INTRODUCTION

In 1915, Hunner (Boston) described "a rare type of bladder ulcer", that is "areas of hyperaemia which, on being touched with a dry cotton pledget bleed and first show their character as ulcers"[1]. The symptoms in the (female) patients were urge, frequency and suprapubic pain. Patient age was 20 to 40 years. This complex of symptoms and characteristic cystoscopic findings is currently recognised as interstitial cystitis and the study by Hunner has become the most frequently cited among articles on interstitial cystitis. Despite the long standing recognition of interstitial cystitis, there are still no definite answers to vital issues such as its etiology, prevalence, diagnostic definition and therapy. Patient advocate groups in the United States have generated recognition, and there has been an exponential growth in clinical and basic research since the 1980s. In contrast to the situation in the United States, epidemiological data and research on interstitial cystitis are severely lacking in Europe. However, interstitial cystitis is a major health problem and is one of the most frequent benign indications for cystectomy, and 50% of the patients are declared unfit to work[2]. It will be necessary to identify and group interstitial cystitis patients for a greater insight into the condition and to develop effective management regimens.

A population-based study to determine the prevalence of interstitial cystitis would require a large sample of patients because of the low frequency of interstitial cystitis in the general population. A patient-based study is not possible because of the absence of an organised registry for interstitial cystitis or a patient association. However, it can be expected that with time all interstitial cystitis patients will consult a urologist because of the severity of the complaints. Therefore, we decided to conduct a survey among all urologists in The Netherlands, including a questionnaire, and registration of the most common diagnostic and therapeutic approaches.

METHODS

A questionnaire was developed in cooperation with the department of epidemiology of our university. The face-validity of the questionnaire was evaluated by sending it to all staff members at the urology department and their comments were used to compose the final version. The questionnaire was then sent to all Dutch urologists. The majority of the questions were precoded and the survey was anonymous.

The questionnaire had three parts: 1) epidemiological section- urologists were questioned for the average number of patients seen per year with chronic micturation disorders, and the number, average age and gender of interstitial cystitis patients treated, with additional information was

obtained on the disease history and presenting symptoms in interstitial cystitis patients, 2) diagnostic section- questions were asked regarding diagnostic investigations and diagnostic criteria for interstitial cystitis patients, and 3) therapy section- urologists were questioned on the most common therapy modalities, and were asked to indicate the first, second and third choices. If surgery was performed, they indicated the preferred surgical technique. All urologists indicated which regional cancer registration center applied to their hospital. In this manner, potential regional differences in prevalence rates, and diagnostic and therapeutic practices could be detected. In addition, all urologists were asked to provide an estimate of the annual number of new cases of prostate cancer and bladder cancer seen in practice. The number of cancer cases in each region could be calculated from these data and compared to the official statistics given by the cancer registry, which provided an indication of the urologist reliability in estimating the prevalence of interstitial cystitis in The Netherlands.

RESULTS

Questionnaires were sent to 235 urologists and 153 were returned, for a response rate of 65%. All data were used to estimate the prevalence of interstitial cystitis. No cases of interstitial cystitis were reported on 21 questionnaires, which along with 10 incomplete questionnaires, were excluded from further analysis. The remaining 122 questionnaires were used to analyze additional epidemiological, diagnostic and therapeutic data using a statistical computer program.

A total of 97 urologists treated 1 to 5 , 20 treated 5 to 10 and 5 treated 10 to 15 interstitial cystitis patients per year. The calculated prevalence of interstitial cystitis was 8 to 16 cases per 100,000 females. Extrapolation to the general population produced an expected group of 400 to 1,300 interstitial cystitis patients. Interstitial cystitis comprised 10% of all chronic functional micturation disorders. The correlation between the urologist-based estimates of (new) prostate and bladder cancer cases and the cancer registry rates were fairly good (0.87 for bladder cancer and 0.64 for prostate cancer).

Only 48% of the respondents reported interstitial cystitis in male patients, with a male-to-female ratio of less than 1:10. Analysis showed that 93% of interstitial cystitis patients were 20 to 60 years old and 91% had a disease history of 1 to 5 years. The most frequently reported symptoms of interstitial cystitis were frequency in 87% of the patients, pain relieved by emptying the bladder in 61%, suprapubic pain in 61% and urge in 57%. When interstitial cystitis was suspected the main investigations were urine culture or urine cytology studies (more than 90%) followed by cystosco-

py with or without biopsies and cystometrograms. Ultrasound and x-ray examinations comprised less than 40% of the studies.

Table 1.

DIAGNOSTIC CRITERIA FOR INTERSTITIAL CYSTITIS urologist-based questionnaire, The Netherlands	
PATHOLOGY OF BLADDER BIOPSIES	91%
HISTORY AND VOIDING LOG	83%
MAST CELLS IN BLADDER BIOPSIES	79%
CYSTOSCOPY UNDER ANAESTHESIA	63%
CYSTOSCOPY	56%
URODYNAMIC INVESTIGATION	55%
NIH CRITERIA United States	26%

Table 1 shows the various criteria used to diagnose interstitial cystitis. Pathology on bladder biopsies was reported most frequently (91%) and slightly more often than was a typical disease history (83%). The presence of mast cells in bladder biopsies was used as a diagnostic criterion by 79% of the urologists, while only 26% applied the United States National Institutes of Health (NIH) criteria. In most cases, a combination of three or more criteria had to be fulfilled to establish a definite diagnosis of interstitial cystitis: 9 urologists (7%) used two criteria and four (3%) used only 1 criterion (mast cells in 2 instances, histology in 1 and cystoscopy with the patient under anesthesia in 1).

A wide variety of therapies were applied (table 2). Dimethyl sulfoxide instillations and prolonged static bladder hydrodistension (Helmstein method) were used by 80% of the urologists. Miscellaneous therapies consisted mainly of non-steroidal anti-inflammatory drugs, anti-cholinergics and prolonged antibiotic courses. If conservative treatment failed, 88% of the urologists considered surgery as optional therapy. However, the number of interstitial cystitis patients finally undergoing surgery varied from 0% (18% of urologists) to more than 50% (9% of urologists). Augmentation

ileo-cystoplasty (39%), subtotal cystectomy with entero-cystoplasty (34%), total cystectomy with urinary diversion (23%) and urinary diversion only (4%) were the preferred surgical techniques. A few urologists (11%) performed surgery as the first or second treatment option.

Table 2.

TREATMENT MODALITIES USED FOR INTERSTITIAL CYSTITIS urologist - based questionnaire, The Netherlands	
D.M.S.O. BLADDER INSTILLATIONS	80%
HYDRODISTENSION (HELMSTEIN)	80%
PENTOSANPOLYSULFATE	38%
AMITRYPTILINE	21%
CORTICOSTEROIDS	18%
ANTIPHLOGISTIC INJECTIONS	9%
SILVER NITRATE INSTILLATIONS	5%
CATHETER	1%
MISCELLANEOUS	25%

DISCUSSION

From a urologist-based questionnaire the prevalence of interstitial cystitis in the Netherlands was estimated to be 8 to 16 cases per 100,000 females. Extrapolated to the entire population yielded approximately 400 to 1,300 (symptomatic) interstitial cystitis cases. However, the reported cases were estimates. To assess the accuracy of the urologist's estimates they were also asked to estimate the number of (new) prostate and bladder cancer cases in 1992. The actual number of prostate cancer and bladder cancer cases (incidence figures for 1992) were provided by the regional cancer registries. Estimated numbers and registered numbers correlated fairly well (0.87 for bladder cancer and 0.64 for prostate cancer). These findings support the reliability of the calculated prevalence in this study. However, the interstitial cystitis estimates mainly reflect the number of interstitial cystitis

patients who consulted a urologist in 1993. The total number of interstitial cystitis patients would be much larger if those who had undergone bladder substitution therapy in the past and those who withdrew from treatment were included. Therefore, the calculated prevalence is probably a conservative estimate.

Studies on interstitial cystitis prevalence are rare. The most frequently cited was a regional population-based study performed in Finland in 1975, which reported a prevalence of interstitial cystitis of 18.1 per 100,000 women[3]. A similar figure (patient-based estimate) was reported at a third line referral (university) hospital in Sweden[4]. Prevalence figures for the United States are mainly based on the study by Held et al (30 per 100,000 male and female patients)[2], which is almost double the prevalence rates reported in Europe [3,4]. A recent study in the United States claimed a prevalence that was 10 times higher than the aforementioned European figure [5]. How should one interpret the lower European prevalence estimates compared to those in the United States? There are 3 possible explanations: 1) the study methodologies may have differed, 2) there may be a genuine difference in prevalence between Europe and the United States and 3) different definitions may have been used. Explanation 1 refers to differences in methodology. Population-based questionnaire studies, as used in the United States, may easily have included patients with symptoms that resembled interstitial cystitis but who were not diagnosed as having interstitial cystitis. However, also in the urologist-based study by Held et al, the prevalence rate in the United States was twice as high as the European figures[4]. Explanation 2 refers to a genuine difference in prevalence between Europe and the United States. However, to date no geographical factor has been reported to influence interstitial cystitis and the preference among the white interstitial cystitis patients should cause rather an opposite genuine difference. Explanation 3 was a possible difference in the definitions of interstitial cystitis. In the United States clinical inclusion and exclusion criteria to define the diagnosis of interstitial cystitis were formulated in 1988[6,7] and are presently being used by the majority of urologists. Our study revealed that general and specific (mast cells) pathological features of bladder biopsies are the most important diagnostic criteria being used by Dutch urologists. The ratio of mast cells as a diagnostic marker for interstitial cystitis has been criticized in the past[8,9]. However, in our study almost 80% of Dutch urologists used mast cells as a diagnostic criterion. If too much weight is placed on the outcome of a single investigation other positive findings may be overruled, causing the under-diagnosis of interstitial cystitis and, therefore, explaining the difference in prevalence between The Netherlands (Europe) and the United States. Explanation 3 probably is the most convincing. In addition, one may speculate about a difference in

awareness concerning the diagnosis of interstitial cystitis. In the United States, an active Interstitial Cystitis Association exists for patients and physicians, which association encourages awareness, information, education and research on interstitial cystitis. It forms a tight network of support for patients and assists physicians once the diagnosis of interstitial cystitis has been esta-blished. These conditions are virtually nonexistent in Europe. Less awareness and, in addition, a bleak prognostic perspective once the diagnosis has been made may cause a vicious circle resulting in a restrictive policy for diagnosis of interstitial cystitis. As reported in our questionnaire, the symptoms presented by interstitial cystitis patients, their age at diagnosis, the female-male ratio and disease history were in line with those reported in other European and American studies[8,10-13].

Approximately 90% of Dutch urologists used 3 or more criteria to diagnose interstitial cystitis, while 26% used the interstitial cystitis criteria as defined by the NIH of the United States[6]. A small group of 13 urologists used 2 (9) or only 1 (4) diagnostic criterion. However, this subgroup did not show any consistent preference for any single criterion.

Although a wide variety of oral and intravesical therapeutic possibilities are available [10,14,15], Dutch urologists appeared to follow a fairly uniform therapy policy. Of the Dutch urologists 50% preferred dimethyl sulfoxide instillations as the initial treatment option, while 30% used dimethyl sulfoxide as a second or third line treatment. The same findings applied to prolonged, static bladder distension. Although the efficacy of hydrodistension according to Helmstein has been questioned by some[16], it proved to be a rather popular treatment in The Netherlands. Treatment policy was not influenced by difference in geographical region, diagnostic criteria or number of interstitial cystitis patient consultations per year.

Surgery was considered by 88% of the urologists as a (final) treatment option. In contrast, 18% of the urologists reported not ever performing surgery on interstitial cystitis patients. This differen-ce could be the effect of asking for estimations on a questionnaire instead of performing a thorough retrospective study. In addition, 39% of the urologists performed surgery in 5%, 26% in 5 to 25%, 8% in 25 to 50% and 9% in more then 50% of the interstitial cystitis patients. No significant differences between the subgroups and the total group existed concerning region, number of interstitial cystitis patients treated in 1993 or diagnostic criteria used. It was not possible to determi-ne the success rate of surgery. The use of different surgical techniques reflects the controversies reported in the literature[17,18].

CONCLUSIONS

The prevalence of interstitial cystitis in the Netherlands is estimated at 8 to 16 cases per 100,000 female adults, which probably is a conservative estimate since only interstitial cystitis patients who sought treatment were reported. Mast cells had an important role in the diagnosis of interstitial cystitis and were reported by 80% of the Dutch urologists as a diagnostic criterion. Difference in definition and awareness of interstitial cystitis could explain the difference in prevalence of interstitial cystitis. Dimethylsulfoxide instillations and hydrodistension of the bladder were practised by more then 80% of the Dutch urologists. This fairly uniform therapy preference demonstrates a remarkable consensus among Dutch urologists concerning interstitial cystitis.

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CHAPTER 3

INCREASED URINARY LEVELS OF TAMM-HORSFALL GLYCOPROTEIN SUGGEST A SYSTEMIC ETIOLOGY OF INTERSTITIAL CYSTITIS

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Abstract.

Purpose. To investigate the role of Tamm-Horsfall protein (THP) in interstitial cystitis (IC).

Materials and Methods. Analysis of urinary Tamm-Horsfall protein excretion in interstitial cystitis patients and control patients. Immunohistochemical staining of bladder biopsy specimens for THP.

Results. Urinary THP levels of female IC patients (n=28) were statistically significantly higher than those of female controls (n=25). No positive staining for THP could be demonstrated in the bladder tissue of the IC patients (n=10).

Conclusions. The results support the notion that the IC syndrome may have a systemic etiology. In addition, this type of assay might have clinical value in the diagnosis of IC.

INTRODUCTION

In 1950 two virologists, Tamm and Horsfall[1], discovered a glycoprotein that now bears their names. Tamm-Horsfall Protein (THP) is the most abundant protein in normal urine and a major component of tubular and urinary casts. THP is synthesized exclusively in the kidney. It has a subunit size of approximately 100,000 Daltons but also a strong tendency to form macroaggregates of several million Daltons. The 24-hr quantity of THP excreted by human individuals has been reported to be 39 mg (+/- 13 mg) and is not influenced by exercise, age or diuresis[2]. THP is essentially localised in the cells of the thick ascending limb of Henle's loop. Two hypotheses have been put forward about its function: (1) THP could be a co-transporter of electrolytes and (2) THP could be responsible for the water impermeability of the nephron segment due to its ability to form gels[3]. Several pathophysiological actions have been suggested. For instance, THP was found to bind to E Coli bacteria which should prevent the adhesion of bacteria to the urinary epithelium[4]; THP seems to be a constant component of renal stones; and interstitial nephropathy was demonstrated in experimental rat and rabbit models after active immunisation with THP[5].

Interstitial cystitis (IC) is a chronic benign disease of the bladder, that mainly affects women and has debilitating symptoms. The origin of interstitial cystitis is unknown. Currently, there is no compelling evidence to support any of the hypothetical causes. Studies that demonstrate intra-urothelial THP and elevated levels of antibody to THP in IC patients seem to confirm the theory of increased bladder permeability to urinary constituents as the etiological mechanism of IC and to offer a possible diagnostic marker[6,7]. However, more recent studies have contradicted previous reports[8,9]. A possible pathophysiological relation between Tamm-Horsfall protein and interstitial cystitis remains speculative and, as such, forms a challenge.

This study investigates the THP excretion of IC patients compared to controls. In addition, bladder biopsy specimens of IC patients have been examined for possible THP deposits.

METHODS AND PATIENTS

Patients. Multiple 24-hour urine samples were collected prospectively from 30 consecutive patients, diagnosed and treated for interstitial cystitis (*IC-patients*) and 46 controls (*Control-patients*). All of the interstitial cystitis patients were diagnosed according to the criteria published by the National Institutes of Health[10] for the admittance of subjects into research studies and were suffering from symptoms typical of interstitial cystitis at the time of urine collection. The average functional bladder capacity of the *IC-patients* was 189 cc (range 70 cc to 385 cc) and their average disease

history 5.6 years (range 2 to 18 years). A functional bladder capacity of above 400 cc formed an exclusion criterion for the diagnosis of interstitial cystitis. The group of controls (Control-patients) comprised patients (n=46) with different urological diseases, shown in *Table 1*.

ELISA assay. Urine samples of 24-hour urine were kept frozen (-20 °C) until use for Tamm-Horsfall protein quantification. Tamm-Horsfall protein determinations were performed on all the urine samples according to a 'blind' experimental design using an in-house ELISA. Anti-THP antibodies and THP standard were purchased commercially. In short, polyclonal sheep-anti-human THP antibody (IgG fraction; The binding Site/Biomedical Diagnostics) was bound to the wells of micro-titre plates. Standards (Calbiochem) and urine samples were incubated at 37°C for 45 minutes. Non-bound material was expelled and after washing, polyclonal sheep-anti-human THP-peroxidase conjugated antibody (the binding Site/BioMedical Diagnostics) was allowed to react at 37°C for 30 minutes. Reaction products were visualised with o-phenylenediamine as the substrate; absorbance was then measured at 492 nm. Reproducibility and the influence of prolonged frozen storage of the urine samples were tested.

Immunohistochemical detection of Tamm-Horsfall protein. Bladder tissue samples were obtained from all 30 IC patients during cystoscopy under anesthesia. The tissue samples were partly frozen (-20^0C) and partly fixed in 10% buffered formalin. The latter samples were embedded in parafin and prepared according to routine light microscopic procedures. Sections (5 µ thick) from 10 interstitial cystitis and 3 control patients were incubated for 60 minutes with the murine monoclonal antibody against Tamm-Horsfall protein diluted 1:1000 in phosphate buffered saline (Sanbio - Uden, the Netherlands). The streptavidine-biotine immunoperoxidase technique was used to identify binding of the monoclonal antibody in the tissue sections. Specificity of the monoclonal antibody for Tamm-Horsfall protein was demonstrated by the immunohistochemical study of normal renal parenchyma using the aforementioned techniques.

Data analysis. Data analysis was performed with the commercial SPSS/PC Statistical Package. The chosen level of statistical significance was $p = 0.05$. Sensitivity was defined as the ability to detect the disease; specificity was defined as the ability to detect the absence of disease; and predictive diagnostic value was defined as the ability to detect patients with the disease (interstitial cystitis) in a given population.

RESULTS

We analysed 101 24-hour-urine collections from 30 interstitial cystitis patients (IC-patients) and 52

24-hour-urine collections from 46 control patients (Control-patients). All 24-hour-urine samples were collected between February 1993 and February 1995. Average storage time before analysis was 2.2 weeks at -20^{0}C. The IC-patients were 28 females and 2 males with an average age of 55.2 years (24-79 yrs); the control-patients (*Table 1*) comprised 24 females and 22 males with an average age of 56.3 years (4-82 yrs). Creatinine clearance of all patients (based on serum creatinine, age and weight) was within the normal range.

Table 1.

DIAGNOSES OF THE CONTROL PATIENTS (MALE AND FEMALE).

DIAGNOSIS:	CONTROL-PATIENTS:
urinary tract infection	n=12
supravesicular obstruction	n=7
urinary diversion	n=6
infravesicular obstruction	n=4
urolithiasis	n=4
invasive bladder carcinoma	n=3
renal adenocarcinoma	n=3
superficial bladder carcinoma	n=3
vesico-ureteral reflux	n=2
pyeloureteral stenosis	n=2
	n=46

To prevent selection bias we used the first urine sample test result of each patient for statistical analysis. Tamm-Horsfall concentrations in both groups showed a skewed distribution and a considerable range, reflected in high standard deviations. This violated the pre-assumptions for using Student's t-test. Therefore, the non-parametric Mann-Whitney test was used to determine statistical significance. Analysis for age did not show a correlation between THP excretion and age. A similar analysis for gender showed a significantly higher THP excretion in the female patients than in the male patients, conform to the predominance of females among IC-patients. However, urinary THP

levels were also higher among female Control-patients (mean 25.2 mg/l and 42.7 mg/24 hrs) than those of the male patients (mean 14.8 mg/l and 26.4 mg/24 hrs). Although these differences were - not statistically significant (p=0.208 for mg/l and p=0.496 for mg/24hrs, Mann-Whitney test), we decided to include only female patients in the further analyse.

The individual and mean values for urinary Tamm-Horsfall protein excretion, expressed in concentration (mg/l), total amount (mg/24-hrs) and related to creatinine (µg/mg creat) are shown in *Figure 1*, *Figure 2* and *Figure 3*, respectively. Differences between IC-patients and Control-patients were statistically highly significant with p=0.006 (mg/l), p=0.003 (mg/24 hrs) and p=0.002 (µg/mg creat.). To evaluate the value of THP excretion as a diagnostic marker, we used 'normal' excretion values 40 mg/24 hrs or 40 µg/mg creat. as cut-off values. Distribution and percentages are presented in *Table 2*. Sensitivity was 67%, predictive diagnostic value was 67% and specificity was 78%.

Table 2.

Tamm-Horsfall protein excretion using cut-off values of 40 mg/24hrs and 40µg/mg creat., and statistical significance using the Chi-square test.

	IC-PATIENTS	CONTROLS	Chi-square test
> 40 MG/24 HRS	n=20 (71.4 %)	n=6 (25.0%)	
≤ 40 MG/24 HRS	n=8 (28.6%)	n=18 (75.0%)	p < 0.0001
> 40 µG/MG CREAT.	n=17 (60.7%)	n=6 (25.0%)	
≤ 40 µG/MG CREAT.	n=11 (39.3%)	n=18 (75.0%)	p < 0.0001

Differences between infection (positive urine cultures) and non-infection patients, and between stone and non-stone disease were not significant. In three patients with renal adenocarcinoma, THP excretion was 14 mg/24 hrs, 50 mg/24 hrs and 57 mg/24 hrs, respectively. In two control patients, THP excretion levels of over 100 mg/24 hrs were detected. One was diagnosed as having an obstructed ureter and was known to have SLE and rheumatism, while the second patient was diagnosed as having a pyobladder.

To rule out storage artefacts, 5 urine samples were stored at either -20^{0}C or -80^{0}C and analysed at 2, 4, 7, 9 and 12 weeks. Low THP concentrations (<25 mg/l) remained almost stable at different temperatures and after different storage intervals. High THP concentrations (>50 mg/l) fluctuated by up to 50% at -20^{0}C, and by up to 40% at -80^{0}C, but only after storage for more than 4 weeks. Values fluctuated between 0% and 22% after storage at -20^{o}C for less than 4 weeks.

The bladder biopsy specimens of only one of the ten IC patients stained weakly positive for THP. Control staining of normal renal parenchyma was highly positive.

DISCUSSION

In a prospective study on urinary Tamm-Horsfall protein (THP) excretion, a significant difference was detected between (female) interstitial cystitis patients (n=28) and (female) controls (n=25). Despite the increased values, no Tamm-Horsfall protein bladder depositions could be demonstrated.

Urinary excretion of Tamm-Horsfall protein has previously been linked to uro-pathological conditions. Its potential role, stimulation or inhibition, in stone formation was studied in the late seventies but no increase in THP urinary excretion could be detected in individuals with bladder or renal urolithiasis when compared to healthy controls[11,12]. More recently, the inhibitory effect of potassium citrate treatment on calcium oxalate monohydrate crystal agglomeration was associated with increased levels of THP[13]. Reinhart et al. studied THP as a potential urinary defense mechanism against urinary tract infections. A decrease in THP urinary levels was reported in elderly patients especially during episodes of urinary tract infection[14]. This could not be reproduced in young women with and without recurrent urinary tract infections[15]. Urinary excretion of Tamm-Horsfall protein in interstitial cystitis patients was reported only once. Callahan et al. could not demonstrate a difference between IC patients and controls, but only random urine samples were analysed (µg THP per mg creatinine)[16]. In contrast to the latter study, our data, based on 24-hour-urine collections, demonstrated increased THP urinary levels in interstitial cystitis patients; in absolute values as well as in relation to creatinine excretion. These differences were statistically significant. A clear explanation for this increase is not readily at hand.

A number of factors are thought to influence the quantity of Tamm-Horsfall protein measured in urine. These include aggregation of the glycoprotein, alkalisation of urine, storage artefacts and difference between the sexes[2,3,13,17]. Gender was also observed to have an influence in our Control-patients. As the *IC-patients* mainly comprised female patients, we excluded all the male patients

from the statistical analyse to achieve a genuine comparison between controls and IC patients. *IC-patients* and *Control-patients* were compatible with respect to age, renal function and urine pH. No positive correlation could be detected between urinary THP levels and urine culture results. Sixteen of the *IC-patients* underwent a detailed dietary interview which did not reveal any self-imposed specific dietary restrictions or avoidance of certain foods. A separate study was conducted to control for possible storage artefacts and showed that these could be excluded as possible causes of the difference in values between *IC-patients* and *Control-patients*. Presumably, if circumstances beyond our observation influenced the measurements, they did so in both groups. Thus, the difference in THP most probably reflects the difference in pathology between the two groups: interstitial cystitis.

Increased Tamm-Horsfall protein excretion in interstitial cystitis patients raises two questions. First, could the THP urine level function as an objective criterion or parameter in diagnosing IC? and second, how should one interpret the relation between THP urinary excretion and interstitial cystitis, as coincidental or causal?

At present, the diagnosis of interstitial cystitis is based on clinical criteria, without a reliable diagnostic marker. However, by using 40 mg/24 hrs and 40 µg/mg creat. as cut-off values, the sensitivity (67%) and predictive diagnostic value (67%) of THP failed to meet the ideal 100%. Although not (yet) suitable as a diagnostic marker, THP urine levels might be used as an additional positive indication for the diagnosis of interstitial cystitis.

The second question addresses the hypothetical explanation of the registered increment of urinary Tamm-Horsfall protein. Should it be regarded as being coincidental, or causative or reactively related to IC? The former seems unlikely in view of the statistical significance of the difference between the female patient groups. Only a speculative answer can be given to the second part of the question. Nevertheless, if increased THP excretion can be attributed to interstitial cystitis, it would suggest a causative relation because, according to present physiological knowledge, a bladder-confined disease has no feedback mechanism to the kidney and THP is solely produced in the kidney. THP levels might increase in combination with other, yet unknown, toxic urinary agents which cause or contribute to the symptoms of IC[18]. Or a systemic, i.e. an auto-immune disease may cause asymptomatic interstitial nephritis which is known to cause an increase in the THP level[3,5]. In animal experiments, an inflammatory reaction to THP has been observed, but a direct relation between an increased urinary THP level and bladder symptoms has never been reported. It has been suggested that increased permeability allows THP to infiltrate bladder tissue and may lead to

sensitisation to this protein. However, our data did not support this theory. In our patients, an increased urinary THP concentration was not associated with THP infiltration of bladder tissue. In addition, Thruong et al. reported on 18 cases with Tamm-Horsfall protein deposits in a series of 262 bladder specimens[19]. Most deposits were related to carcinoma of the bladder, six to chronic cystitis and none to interstitial cystitis.

CONCLUSIONS

The increased urinary THP levels in interstitial cystitis patients support the etiological theory of a systemic disease and may offer new perspectives as diagnostic indicator for the diagnosis of the interstitial cystitis syndrome.

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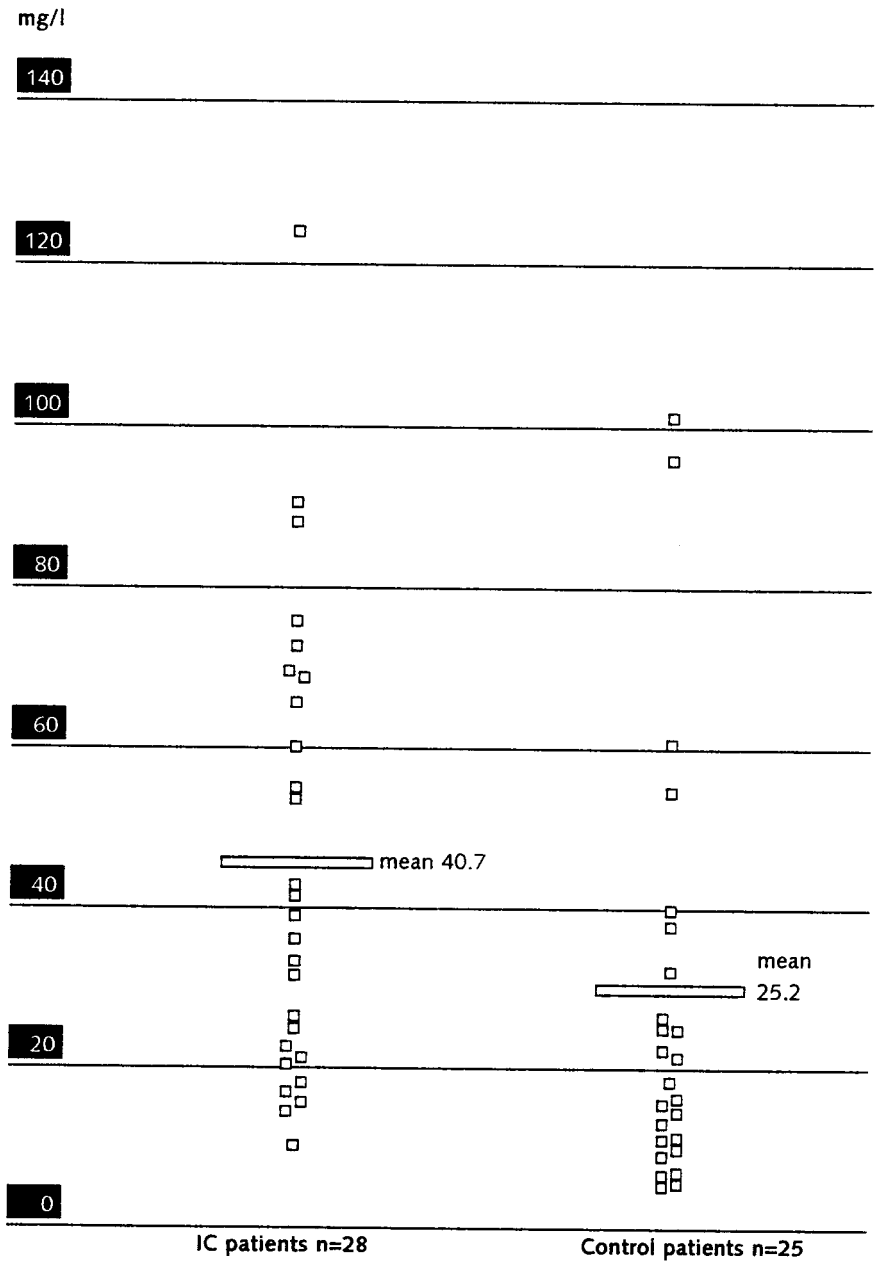

Figure 1

Individual and mean urinary Tamm-Horsfall protein (THP) concentration. The (female) IC-patients excreted a mean 40.7 mg/l (S.D. 26.5) and the (female) Control-patients a mean 25.2 mg/l (S.D. 25.1). The difference was statistically significant (p=0.006) using the Mann-Whitney test.

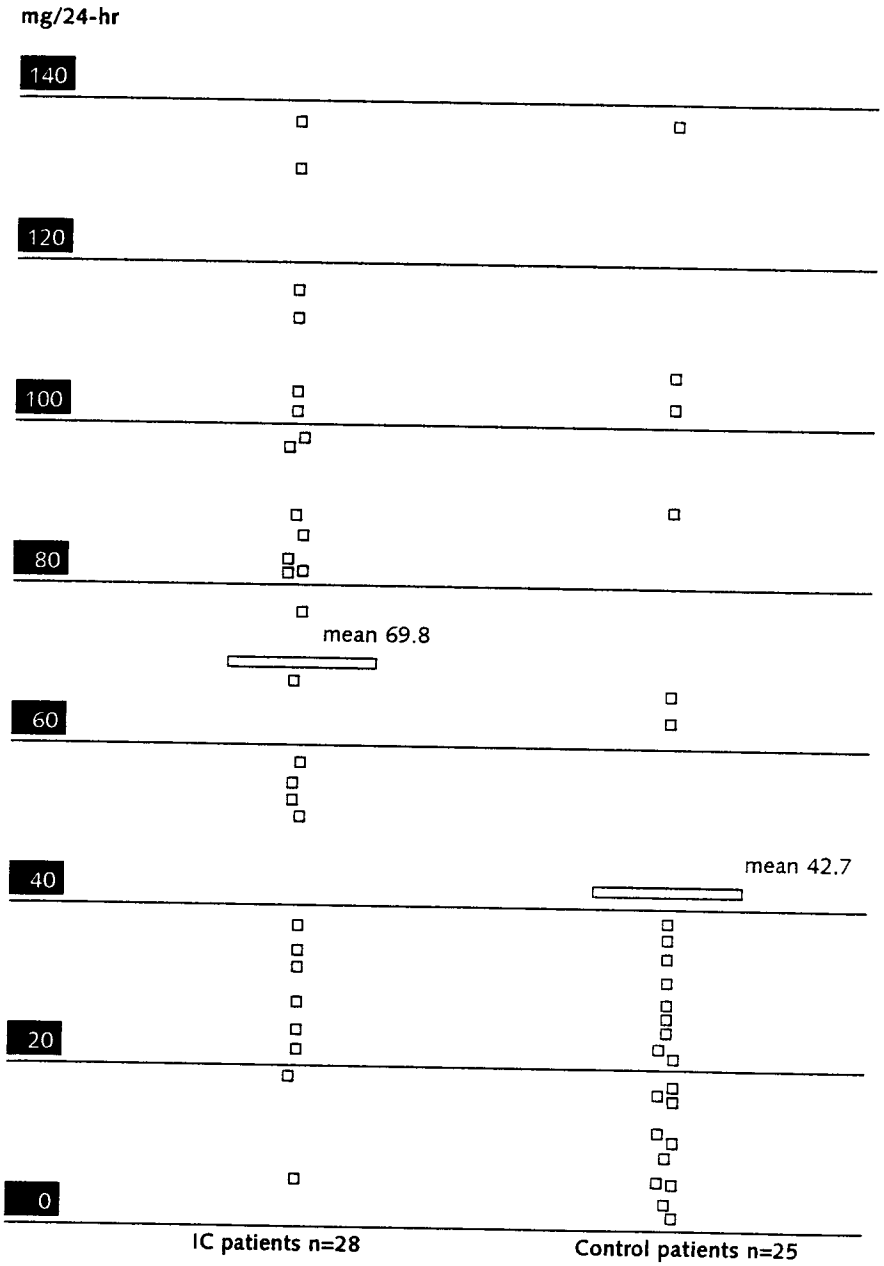

Figure 2

Individual and mean 24-hour urinary Tamm-Horsfall protein (THP) excretion. The (female) IC-patients excreted a mean 69.8 mg/24 hrs (S.D. 35.5) and the (female) Control-patients a mean 42.7 mg/24 hrs (S.D. 49.0). The difference was statistically significant (p=0.003) using the Mann-Whitney test.

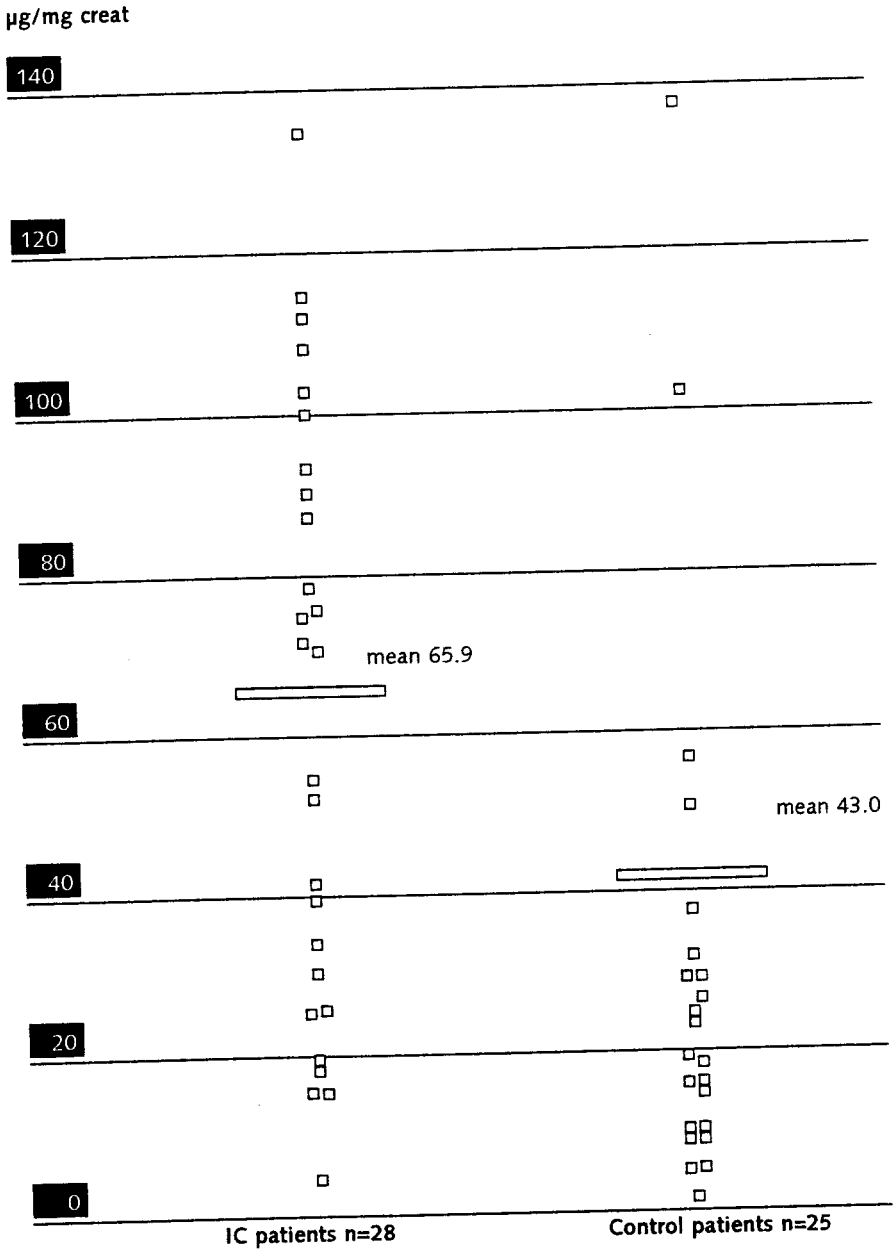

Figure 3

Individual and mean urinary Tamm-Horsfall protein (THP) excretion related to the creatinin concentration. The (female) IC-patients excreted a mean 65.9 µg/mg creat. (S.D. 46.9) and the (female) Control-patients a mean 43.0 µg/mg creat. (S.D. 61.4). The difference was statistically significant (p=0.002) using the Mann-Whitney test.

CHAPTER 4

DEMONSTRATION OF SPECIFIC AUTO-ANTIBODIES ADD NEW EVIDENCE TO AN AUTO-IMMUNE PATHOGENESIS OF INTERSTITIAL CYSTITIS

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Submitted

Read at:

The Fourth International Meeting of the Dutch Society for Urology, Nijmegen, The Netherlands, November 1995.

The annual meeting of the American Urological Association, Orlando, USA, May 1996.

Abstract:

Background. Interstitial cystitis (IC) is a long recognised, chronic benign bladder disease with debilitating symptoms. The disease has by definition an inflammatory nature, but its cause and etiology are still unknown.

*Methods.*Antibodies were isolated from three, randomly chosen, sera taken from IC patients. After labelling with biotin these antibodies were applied to sections made from autologous or heterologous bladder tissue. Binding of the biotinylated antibodies was visualised with a streptavidine-peroxidase staining procedure.

Results. We demonstrated the presence of specific auto-antibodies in all (n=3) tested IC patients. The auto-antibodies were directed against epithelium and muscle fibers of the bladder wall. Bladder tissue treated with control serum showed no response.

Conclusions. The in the present study employed direct immunostaining procedure shows the presence of auto-antibodies that have not been reported before in relation with interstitial cystitis. The specific auto-antibodies demonstrated in this study indicate the involvement of an auto-immune reaction in the pathogenesis of interstitial cystitis. If future studies confirm these findings it might cause a breakthrough in the understanding and treatment of this disabling, chronic bladder disease.

The following presentations were based on this chapter:

Presentation D.U.A. (Dutch Urological Association) Nijmegen, November 1995.

Presentation A.U.A. (American Urological Association) Orlando, May 1996.

INTRODUCTION

Interstitial cystitis (IC) is a chronic idiopathic inflammatory bladder disease. Most patients report a subacute onset with similar symptoms as a urinary tract infection, some relate the start of symptoms to a preceeding event, i.e. hysterectomy or post-operative urine retention. The symptoms pain, frequency of micturation and nocturia usually fail to respond to regular treatment with antibiotics after which the disease takes a chronic course. Many studies were set up to detect a causitive infectious microorganism but proved to be negative[1]. Unfortunately the diagnosis IC is often overlooked, even by urologists. Misdiagnosis, inappropiate surgery to relief the pelvic pain, and social isolation contribute to the chronic debilitating course of the disease. Eventually, some type of surgery is performed in 10 - 40% of the IC patients to achieve symptomatic relief. A substantial minority ends up with a permanent abdominal urostoma, which reflects the persistence and severity of symptoms caused by this benign bladder disease.

The typical clinical findings in IC, suprapubic or perineal pain combined with frequency of micturation and nocturia, were first reported in detail by C.L. Hunner in 1914, describing a series of female patients between 20 and 40 years[2]. These characteristic symptoms combined with the typical mucosal lesions of the bladder have remained the mainstays of diagnosis in IC. Largely due to efforts of patient advocate groups in the USA awareness for this mysterious bladder disease has increased. Epidemiological studies revealed unexpected large numbers of patients suffering from interstitial cystitis. At present prevalence of IC in the USA approximates a 500.000 cases and is considered a major health problem[3,4]. Despite an exponential growth in clinical and basic research in the past decennium, there are still no definite answers to vital issues such as the etiology of IC.

Today the general opinion is that the etiology of IC is multifactorial. Infection, deficiency in the bladder glycosaminoglycan layer, toxic agents in the urine, local neuropathic mast cell stimulation in the bladder, and auto-immune reactions have been suggested as possible etiologic causes[5]. Non-consistancy of pathological and serological findings indicating an auto-immune reaction in combination with the variable responses to immunosuppressive treatment have been interpreted as an argument against a possible autoimmune pathogenesis of IC[6]. However, many facets of IC are similar to well-known auto-immune diseases. Firstly, 90% of the patients is female, with a preferential age between 20 and 60 years. Secondly, the episodic waxing and waning of the disease. Thirdly, the onset of disease is often well memorised by patients even after many years, which indicates a subacute onset[7,8]. Fourth, histopathological examination of the bladder wall shows the localised presence of dense mononuclear infiltrates in which lymfocytes are abundantly present. The

demonstration of mast cells is characteristic in these biopsies[9]. Fifth, a considerable number of IC patients has been co-diagnosed with well-known auto-immune diseases, i.e. lupus erythematosis, polyarteritis nodosa, rheumatoid arthritis, ulcerative colitis and M. Sjogren[8,10,11].

This study was designed to evaluate the presence of tissue-specific auto-antibodies in IC patients using a direct immunostaining technique not reported before in relation with IC patients.

MATERIALS AND METHOD

Peripheral blood samples were obtained from 20 consecutive interstitial cystitis patients participating in a placebo controlled therapeutic trial. All patients were diagnosed as having IC in accordance with the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (USA) criteria[12]. All patients participated in a placebo-controlled study on the efficacy of pentosanpolysulfate intravesical instillations for the treatment of IC. Serum was collected before initiation of treatment and stored frozen at -20^{o}C. In addition, coldcup bladder biopsies of each IC patient were snap-frozen in methyl-butane (-80^{0}C) and stored at -80^{0}C until use. The biopsies were used for standard histopathological examination and partly for the present study. The control serum sample consisted of pooled serum from 20 normal, healthy individuals. Sera samples of 3 IC patients were chosen at random. From these sera and the control serum batch. the IgG fraction was isolated by protein-G-column (Pharmacia, Uppsala, Sweden) chromatography. IgG was biotinylated by the addition of NHS-biotin (Pierce, ?, USA) in a mol/mol ratio of 20. Unbound NHS-biotin was removed by gelfiltration (sephadex 650, Pharmacia, Uppsala, Sweden). The final concentration of the biotinylated IgG preparation was set at 1 mg/ml. Various dilutions of these preparations in PBS containing 10% normal human serum were incubated with cryostatsections of bladder tissue. Both, heterologous-normal and autologous bladder tissue was used. The bound antibody-biotin was visualized - with a standard streptavidine-peroxidase (DAKO, Denmark, dilution 1:50) staining using AEC as a substrate. Nuclei were weakly counter stained with haematoxylin. From the sera of the same three IC patients the antinuclear antibodies (ANA) titers were determined, using standard indirect immunofluorescense procedures.

Results

Antibodies isolated from all three IC-patient sera, but not from the control serum, showed a restricted reactivity pattern when tested on heterologous-normal bladder tissue specimens. When sections from autologous bladder biopsies were taken as a substrate similar specificities were noted. The antibodies appeared to react with the epithelial layer as well with muscle filaments. Detailed results are presented in *Table* 1. In one patient (no. 3, *Table* 2) also nuclear staining could be seen.

Table 1

Characteristics of the main immunohistochemical findings and presence of anti-nuclear antibodies (ANA).

	Summary of immunohistochemical findings	Lowest Ig concentration showing positive reaction	Test for anti-nuclear antibodies (ANA)
Patient 1	Transitional Cell layer: positive; muscle: positive; B-cell follicles: some staining	25 µg/ml	Negative
Patient 2	Transitional Cell layer: positive; muscle: positive; B-cell follicles: some staining	25 µg/ml	Homogeneous staining; titer 40
Patient 3	Transitional Cell layer: positive; muscle: positive	100 µg/ml	coarse speckled staining pattern; titer 640

The clinical characteristics of the three IC patients are shown in *Table* 2. The tested IC patients were all 'end stage' patients with limited bladder capacity. Patients number 1 and 3 (*Table* 1) failed to obtain symptomatic relief from conservative treatment options and, eventually, underwent supravesical urinary diversion while the bladder remained in situ. All IC symptoms disappeared completely after urinary diversion. Patient no. 2 achieved only a symptomatic remission with pentosanpolysulfate instillations. One year after the collection of serum, she was treated for an allergic alveolitis caused by nitrofurantoin medication with high dose corticosteroids (Prednisolone). The alveolitis was cured and also caused a return to normal of her micturation frequency and voiding volumes.

The streptavidin-peroxidase mediated staining of the transitional cell layer in autologous bladder tissue following contact with biotinylated Ig isolated from the serum of patient no. 3 is shown in *photomicrograph* 1, while the result after contact with biotiny-

lated Ig isolated from the control serum is demonstrated with *photomicrograph* 2. *Photomicrograph* 3 presents the lamina muscularis in autologous bladder of patients no. 1 after contact with biotinylated Ig isolated from the serum in a magnification of 1:1000.

Table 2

Clinical characteristics of the three interstitial cystitis patients.

	gender	age	disease-history	cystometric capacity	frequency per 24 hr	nocturia
Pt 1	F	75	6 years	210cc	26x	8x
Pt 2	F	60	3 years	125cc	18x	5x
Pt 3	F	35	4 years	75 cc	25x	6x

In two patients (no 1 and 2, Table 2) the presence of antinuclear antibodies (ANA) was demonstrated. Details are presented in Table 1.

Discussion

In this study we demonstrated the presence of specific autoantibodies in all (n=3) tested interstitial cystitis (IC) patients. The autoantibodies were directed against the transitional cell layer and muscle fibres of the bladder wall. Tissue treated with control serum showed no response. No difference was observed between autologous and heterologous bladder tissue. In addition to organ-specific antibodies we detected anti-nuclear antibodies in two out of the three IC patients.

Autoimmune disorders may be characterised by the presence of organ-specific or non-specific antibodies such as antinuclear antibodies. The first bladder-specific auto-antibodies in interstitial cystitis were reported by Silk in 1970[13]. It initiated a decade of intense interest in the study of immune phenomena in IC[14,15,16,17]. Unfortunately, these studies were rather inconsistent in both methodology and results. In addition, the interpretation of these studies is hampered by the absence of uniform diagnostic or histopathological inclusion criteria for the inclusion of interstitial cystitis patients. The study of Ochs et al. in 1994 is the first to employ the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (USA) criteria[17]. However, Ochs et al. tested the presence of specific antibodies on a T24 human epithelial cell line with a negative outcome. The most consistent finding concerning auto-antibodies in IC patients is the presence of ANA[14,16,17,18,19,20]. However, this might be a rather aspecific corollary of auto-immune disease. Due to these negative, inconclusive or aspecific data concerning the presence of auto-antibodies the notion of an autoimmune etiology in interstitial cystitis remained a speculative hypothesis[1].

The findings in this study provide new evidence for an auto-immune involvement in interstitial cystitis. Although not all sera were tested, the positive outcome with the three at random chosen sera should be considered highly significant. In addition, the pattern of reaction was very similar with all three tested sera. Whether the interpretation of this finding hint at a primary or a secundary auto-immune pathogenesis is rather speculative, presently. On the one hand, a primary auto-immune involvement in IC, similar to other organ-specific autoimmune diseases such as thyroiditis and diabetes, is supported by similarities in histopathology. The reduced capacity, high compliance and fibrosis of the bladder in chronic IC patients could also be consistent with a primary auto-immune reaction. And the absence of symptoms in IC patients with in-situ bladder after urinary diversion does not contradict a primary auto-immune origin[19], since symptoms might well be related to a functioning bladder. On the other hand, the subacute onset of the disease could be coherent with a secondary auto-immune response to injury of the mucous lining or the bladder wall. In addition, the urine or agents in the urine of IC patients might be perpetuating a (secondary) auto-immune reaction. Which is in line with the observed allergic skinreactions in human volunteers and cystitis-like features in rats, both after injection with urine from IC patients[21,22].

A possible auto-immune pathogenesis has triggered the use of immunosuppressiva for the treatment of IC long before. In 1971, Badenoch used prednisolone and observed sustained improvement in 19 out of 25 cases[23]. Oravisto, 1976, reported on the use of Azathioprine which banished the symptoms almost completely in 22 out of 38 patients[24]. Other reports on the use of immunosuppressiva in IC patients are largely anecdotal case-reports[1,6,19,25]. The potential dangerous side-effects of these medicines might be explanatory and indeed, warrant a solid pathogenetic-based indication for a properly designed study.

CONCLUSIONS

To our knowledge, the direct immunostaining procedure employed in this study has not been reported before in relation with interstitial cystitis. The specific auto-antibodies demonstrated in this study indicate the involvement of an auto-immune reaction in the pathogenesis of interstitial cystitis. If future studies confirm these findings it might cause a breakthrough in the understanding and treatment of this disabling, chronic bladder disease.

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Photomicrograph 1

Streptavidin-peroxidase mediated staining of the transitional cell layer in autologous bladder tissue following contact with biotinylated Ig isolated from the serum of patient no. 3.

Photomicrograph 2

Streptavidin-peroxidase mediated staining of the transitional cell layer in autologous bladder tissue from patient 3, following contact with biotinylated Ig isolated from the control serum.

Photomicrograph 3

Magnification of 1:1000 from streptavidin-peroxidase mediated staining of the *lamina muscularis* in autologous bladder tissue following contact with biotinylated Ig isolated from the serum of patient no. 1.

CHAPTER 5

TREATMENT OF INTERSTITIAL CYSTITIS WITH INTRAVESICAL PENTOSANPOLYSULFATE: A PILOT-STUDY

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British Journal of Urololgy 1995; 75: 260.

Abstract:

Objective: To investigate the therapeutic efficacy and side effects of Pentosanpolysulfate intravesical application in interstitial cystitis (IC) patients.

Patients: Six, consecutive, IC patients received 300 mg Pentosanpolysulfate intravesical, twice in a week.

Results: After a mean follow-up of 21 (16-25) months, four out of six patients attained an almost complete symptomatic relief and objective remission. Self-catheterisation enabled long-term treatment with minimal inconvenience. Excellent tolerance was noted in all patients.

Conclusion: Efficacy and safety of intravesical pentosanpolysulfate in the treatment of interstitial cystitis was demonstrated. Prolonged instillations provided a sustained remission. Future controlled studies should confirm these observations and determine the optimal dosage.

INTRODUCTION

Interstitial Cystitis (IC) is manifested by a symptom complex of significant frequency, urgency and suprapubic pain. Traditional, therapy for interstitial cystitis has been clinically and scientifically unsatisfactory. Many regimens have been heralded in preliminary reports, only to be abandoned within several years[1-3].

Surface glycosaminoglycans, the 'mucus' lining of the bladder, have been identified as the defence mechanism coating and protecting the transitional cell surface[4,5]. A current hypothesis of etiology in interstitial cystitis is a defect in the epithelial barrier of the bladder, allowing normal or abnormal substances in urine to gain inappropiate access to the deeper layers of the bladder wall, initiating a circle of irritation, recruitment of immune cells and immune-mediated responses[6]. Experimentally sodium pentosanpolysulfate, a heparin analogue, has been shown to reinforce the glycosaminoglycans and reduce transitional cell injury[7]. These results and theories formed the rationale for use of pentosanpolysulfate in the treatment of interstitial cystitis. However, studies on oral pentosanpolysulfate reported various success rates. In the study by Parsons and associates[8], patients receiving oral pentosanpolysulfate reported an overall improvement of their symptoms compared with the placebogroup ($p<0.05$). Another study produced similar results[9], but a multicenter placebo-controlled trial reported by Holm-Bentzen et al. failed to reproduce these results[10].

In a prospective, clinically controlled, study we attempted to improve the aforementioned therapeutic results by intravesical application of pentosanpolysulfate, and to observe tolerance and side effects.

PATIENTS AND METHODS

The study was approved by the Ethics Committee and informed consent was obtained from each patient. Six, consecutive, interstitial cystitis patients full-filled the diagnostic characteristics set by the National Institutes of Health (U.S.A.) in 1987[11]. No sustained relief had been provided by previous treatments, among them oral amitryptiline, bladder hydrodistension, submucosal heparin injections and DMSO intravesically. Before institution of treatment clinical evaluation comprised a cystometrogram awake (20 cc fill rate per minute), routine laboratory examinations, urine culture and cytology, and cystoscopy under anaesthesia with coldcup biopsies and capacity measurement (1 min. flow, 80 cm H_2O pressure).

At the start and after three, six and 12 months patients were interviewed to evaluate the subjec-tive improvement with a symptom score, similar to the one reported before by Fleischmann et al.[12].

In the doctor-based symptom score scale a numerical value of 0, 1 or 2 was given for the symptoms frequency, urge, nocturia, dysuria and pain: 0-no symptoms, 1-voiding interval between one and two hours, urge exceeding actual frequency, nocturia between one and four times, dysuria intermittent and severe pain, 2-voiding interval less than one hour, constant urge, nocturia more then four times, dysuria at each void and incapacitating pain. The values were added for each patient (minimum 0 and maximum 10). To assess the objective response we performed a cystometrogram after three and 12 months and a 48-hours chart was completed by the patients themselves, every 6 weeks.

Pentosanpolysulfate was commercially ordered (Bayer a.g., München-Germany) as injection fluid vials (100mg/ml). The hospital pharmacy converted them into sterile bladder instillations of 300mg pentosanpolysulfate in 50 cc Urotainer(0,9% sodiumchloride solution). In preliminary tests a volume of 30cc proved too small to garantee efficient instillation. The solution was colourless and without odour. The solution remained stable for one month, stored in a refrigerator. All patients applied intravesical pentosanpolysulfate two times in a week. Instillations were given at the hospital, at home with help of the district-nurse or by self-catheterising after instructions. Patients retained the medication in their bladders for as long as they were able before voiding. Urine samples for culture and cell histology were collected at monthly intervals.

RESULTS

Six (five women, one man) patients with an average age of 57,8 years (range 46 - 64) were included in the study. Mean follow-up was 21 months with a minimum of 16 months and a maximum of 25 months. The average bladder capacity under anaesthesia, at the start of the study, mounted 229cm^3 (range 120-480). The average functional cystometrogram capacity was 165cm^3 (range 50-330) and the volume of 'first desire' 103cm^3 (range 30-275). The average number of voids per 24 hours was 21,6 (range 11 - 40) and per night 4,8 (range 2 -10) with a mean voided volume of 93 cm^3 (range 60 - 200).

The treatment schedule started at the hospital. Eventually all patients employed self-catheterisation. Bladder instillations were collected once every 3 weeks, and stored at home. Originally the study was designed to run for 3 months. At three months four patients reported improvement. Two patients didn't note any relief, neither excerbation, nor side-effects. These two changed to other conservative treatment modalities. One of the two remained with stable disease and one is now eligible for urinary diversion. All four responders experienced a flare-up of symptoms after withdr-

awel of therapy. Consequently, the four responders restarted intravesical pentosanpolysulfate which they continued for a mean 16 months (range 11 - 21).

Table 1 presents the functional (cystometrogram) capacity of each individual patient at the start, three, six and 12 months. The average functional capacity of the four responders improved from 130 cm^3 at the start to 186cm^3 at three months and 250cm^3 at 12 months. *Table 2* shows the individual voiding frequency per 24 hours of each patient. Nocturia changed from an average of 6.0 at the start to 3.2 at 3 months and 2.8 at 12 months, of the four responders. *Table 3* presents the total value of symptom scores of each patient. The average score of the four responders fell from 8.3 points at the start to 4.3 points at 3 months and 3.3 points at 12 months.

Table 1.

Intravesical pentosanpolysulfate therapy. *Cystometric bladder capacity* of each individual patient at the start and after three and 12 months follow-up.

No.	Start	3 months	12 months
Patient 1	110cc	250cc	280cc
Patient 2	213cc	195cc	200cc
Patient 3*	330cc	330cc	*
Patient 4	50cc	80cc	120cc
Patient 5*	140cc	*	*
Patient 6	144cc	221cc	400cc

* non responders who discontinued treatment, no urodynamic follow-up available.

Table 2.

Intravesical pentosanpolysulfate therapy. *Voiding frequency per 24 hours* of each individual patient at the start and after three, six and 12 months follow-up. Frequency was calculated from a 48-hours voiding log.

No.	Start	3 months	6 months	12 months
Patient 1	10x	8x	9x	7x
Patient 2	11x	6x	6x	7x
Patient 3*	16x	15x	18x	19x
Patient 4	22x	16x	14x	20x
Patient 5*	31x	19x	15x	15x
Patient 6	40x	16x	25x	22x

* non responders who discontinued treatment.

Table 3.

Intravesical pentosanpolysulfate therapy. *Subjective symptom score* (between 0 - 10 points, increasing with severity of frequency, urge, nocturia, dysuria and pain) of each individual at the start and after three, six and 12 months follow-up.

No.	Start	3 months	6 months	12 months
Patient 1	9	4	3	2
Patient 2	7	5	4	0
Patient 3*	6	1	2	2
Patient 4	9	2	3	4
Patient 5*	6	7	7	7
Patient 6	8	6	3	7

* non responders who discontinued treatment.

Patients retained pentosanpolysulfate intravesically for as long as urge and pain made it possible. Retention varied from 30 minutes up to almost 120, without any irritative side effects. All urine cultures were negative. Prophylactic antibiotics were not given to female patients, one male patient was advised to take 100mg trimethoprim orally before catheterisation. Treatment of the four responders was discontinued when no further improvement was observed after 11, 14, 18 and 21 months, respectively. All of them sustained remission, thereafter. Two patients were discharged from follow-up after an additional 3 and 7 months, respectively. In one patient, symptoms slowly relapsed after 4 months and he was restarted on intravesical pentosanpolysulfate, now thrice weekly. The fourth patient sustained symptomatic remission, but developed a contracted bladder with bilateral vesicoureteral reflux and detoriation of renal function for which reason a urinary diversion was performed, 4 months after instillations were discontinued.

DISCUSSION

In a prospective, clinically controlled, study with intravesical pentosanpolysulfate four out of six patients attained a symptomatic and objective remission. Tolerance was excellent and no side-effects were observed.

A variety of intravesical instillations have been used in patients with interstitial cystitis. At present DMSO instillation is considered to be the most effective. Although DMSO loses efficacy with time[13]. Short-term successes have been reported with instillations of B.C.G. (Bacillus Clamette-Guérin vaccin) and doxyrubicine[14,15], however only in a very limited number of patients: five and three, respectively.

Most effects of intravesical drugs are explained by diffusion and influenced by concentration, pH and pKa[16]. Pentosanpolysulfate intravesically is believed to reinforce the mucusbarrier complosed of glycoglycans. The exact mechanism and hence the type of action (repair or increased production) remains unknown. In this study two patients did not respond to treatment. A clear explanation is missing. Microscopic differences in bladder biopsies, as reported before[17], could not be demonstrated. Neither do we know if a difference in etiology, i.e. the 'leaky type' versus the auto-immune type, determined non-responders and responders. In four patients a long-term improvement was observed. Reduction of pain sensation was uniformly the first effect. Subjective improvement slowly developed within the first 3 months and was reflected in the objective parameters. Cyclic relapses characterise the natural course of interstitial cystitis. Prolonged treatment not only reduced the severity of these relapses, but also sustained the objective improvement and

further increased the subjective well-being. A similar slow, but steady, improvement was observed with intravesical heparin[18].

Two other important observations were made in this study. The first concerns catheterisation, necessary to use bladder lavages. All patients were instructed in self-catheterisation by experienced nurses. Besides receiving instruction, it gave patients opportunity to discuss their complaints and handicaps with a professional (nurse), familiar with the symptoms of interstitial cystitis and equipped with more time than the doctor. After successful instruction, patients kept returning at a regular basis to obtain new instillations and to have their urine examined. This garantee of regular hospital visits reduced anxiety of patients and encouraged their faith in, eventually, remission. Secondly, side-effects were observed. The main expected side effect, haematuria, attributed to the heparin-like qualities of the drug with prolongation of the prothrombin time, was reported only incidentally after instillation. Catheterisation as well as interstitial cystitis could have caused mild haematuria. There was no causative relation with pentosanpolysulfate. The haematuria always disappeared spontaneouly within 2 days, never necessitating a medical consult. Contrary to other instillation therapies (B.C.G., doxorubicin) irritative voiding symptoms during or after instillation were completely absent.

As long as no effective therapy for interstitial cystitis is available, the general policy of treatment is focused on symptomatic relief and improving of quality of life. Within this policy, absence of (irritative) side-effects should be an important mainstay of new treatment modalities.

CONCLUSIONS

Intravesical pentosanpolysulfate proved an efficient therapeutic modality for interstitial cystitis. Long-term symptomatic relief and objective improvement were observed in four out of six patients. Prolonged treatment reduced frequency of cyclic relapses. Involvement of nurses contributed to the efficacy of treatment and care for the patients with this chronic disease. Future, placebo-controlled studies are necessary to confirm these findings, and to determine the optimal dosis and frequency of instillations.

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CHAPTER 6

A PLACEBO-CONTROLLED STUDY ON INTRAVESICAL PENTOSANPOLYSULFATE FOR THE TREATMENT OF INTERSTITIAL CYSTITIS

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Submitted

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Abstract:

Objective. To evaluate the therapeutic efficacy of intravesical pentosanpolysulfate (PPS) in interstitial cystitis (IC) patients.

Patients and Methods. After a preliminary pilot-study 20 IC patients participated in a double-blind placebo-controlled study with intravesical PPS, applied twice a week, for a period of 3 months. All patients fullfilled the diagnostic NIH-NIADK criteria for IC.

Results. Nineteen patients were evaluable. In the group of patients treated with PPS, 40% experienced symptomatic relief versus 20% in the placebo-group. Only urodynamic bladder capacity showed a statistically significant increase in patients treated with PPS (p=0.047). Following the blinded, controlled period of three months eleven (55%) patients continued PPS instillations. From the group of patients (n=8) who continued with PPS after 3-months-placebo six (75%) reported symptomatic improvement.

Conclusions. We concluded the efficacy of *intravesical* PPS to be slight superior to *oral* PPS. In addition, self-catheterisation enabled long-term treatment and fascilitated the ’self-help’ capacity of IC patients.

INTRODUCTION

Interstitial Cystitis (IC) includes a large group of patients with bladder pain, irritative voiding symptoms (urgency, frequency, nocturia and dysuria) and sterile urine. With little certain about its pathology and etiology a committee convened by the National Institutes of Health has arbitrarily proposed a set of characteristics to define the disease[1]. Despite the exponentional growth in clinical and basic research, no effective standard treatment is available. Small series have reported favourable results with a large variety of drugs, but placebo-controlled studies are rare.

Surface glycosaminoglycans, the 'mucus' lining of the bladder, have been identified as the defence mechanism coating and protecting the transitional cell surface[2,3]. A current etiologic hypothesis of IC is a defect in the epithelial barrier of the bladder, which allows normal or abnormal substances in the urine to gain inappropriate access to the deeper layers of the bladder wall, initiating a circle of irritation and recruitment of immune cells and immune-mediated responses. Experimentally sodium pentosanpolysulfate (PPS), a heparin analogue, has been shown to reinforce the glycosaminoglycans and reduce transitional cell injury[4]. These results and theories formed the rationale to use PPS for the treatment of interstitial cystitis. Different success rates were reported with oral PPS[4 - 9]. In a preliminary pilot study at our centre, pentosanpolysulfate was applied intravesically (300 mg in 50 ml saline 0.9%, twice in a week) instead of orally. Long-term symptomatic and objective remission was observed in four out of the six patients, and tolerance was excellent[10].

Based on these results, a placebo-controlled prospective, double-blind study was designed to evaluate the therapeutic efficacy of intravesical pentosanpolysulfate compared to placebo in IC patients.

PATIENTS AND METHODS

This study was conducted in a double-blind manner, and a placebo control group was used as a comparison. The study was unicentered and approved by the Human Investigation Committee at our hospital. Patients were informed verbally and in written, and informed consent was obtained from each of them. The requested number of patients for each protocol was estimated before the trial on the basis of the results of the preliminary pilot-study; the outcome was 10. The treatment period in both protocols was 3 months.

Patients were recruited from the northern part of the Netherlands, with an estimated population of 1.7×10^6; our university hospital serving as a primary and referral hospital. Before institution of

treatment, clinical evaluation comprised routine laboratory examinations, urine culture, urine cytology, a cystometrogram awake (20 cc fill rate per minute) and cystoscopy under anesthesia with coldcup biopsies and capacity measurement (1 minute at 80 cm H_2O pressure). Patients were selected for enrollment in the study on the basis of inclusion and exclusion criteria as established by the N.H.I. of the U.S.A.[1]. Patients were assigned at random to receive pentosanpolysulfate or placebo in accordance with a random code providing two parallel groups for comparison: a PPS-group and a placebo-group. After receiving treatment for three months the code was broken. All the patients were offered to continue with PPS instillations. Patients who decided to continue received intravesical PPS for at least an additional 3 months. Positive responders were offered to continue arbitrarily up to one year, or to participate in another study evaluating the effect of a change in frequency and composition of the PPS instillations.

Pentosanpolysulfate was ordered commercially (Bayer a.g., München-Germany) as injection fluid vials (100 mg/ml). The hospital pharmacy converted them into sterile bladder instillations of 300 mg pentosanpolysulfate in 50 cc Urotainer (0.9% sodium chloride). The solution was colour-less, without odour and remained stable for a minimum of 6 weeks, stored in a refrigerator. All the patients applied twice weekly intravesical pentosanpolysulfate. The first instillations took place at the hospital and treatment was continued at home by self-catheterisation, after instructions, or with the help of a district nurse. Instillations were collected every 3 weeks at the hospital.

Efficacy evaluation was based on subjective and objective parameters. An overall impression of the symptom-status was recorded at the end of three months. The subjective improvement was evaluated using a visual analoque scale scoring 1 to 5 points. Treatment was considered to be successful if there was a 1-point or greater reduction on the severity scale.

Objective parameters. The 24-hour frequency, the average voiding volume, the maximum volume voided and the nocturia were recorded from a 48-hour voiding chart completed by the patient before treatment started and at 6-weekly intervals. A cystometrogram was performed before installment of therapy and after 3 months, using a flow rate of 20 ml/min. Urodynamic capacity was defined as the voided volume after maximum filling increased with the residual bladder volume. In this way, differences in diuresis during the filling phase were eliminated. Normal desire volume was defined as the feeling that leads the patient to pass urine at the next convenient moment.

Data analysis. Parameters were analysed between the two groups with the Student t-test for independant samples for quantitative variables. Between pre- and posttreatment within the two

groups the Student t-test for matched samples was used. Qualitative variables, improvement or not, were tested with Fisher's exact test. Testing was performed one-sided because greater improvement was expected with PPS than with placebo; $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 20 consecutively diagnosed IC patients were enrolled in the study from May '94 to December '94. All the patients not only met but exceeded the NIH criteria. Despite severe symptoms, only one patient refused to participate in the placebo-controlled study. One patient did not complete 3 months of treatment and was excluded from further analysis. Nine patients received PPS and 10 received placebo. All the patients were women, with an average age of 53.8 years (range 24 - 75 years) in the PPS group versus 52.8 years (range 24 - 79) years in the placebo group. The average duration of the disease was 5.4 years (range 1-18 years) in the PPS group and 4.1 years (range 2-9 years) in the placebo group. Mean bladder capacity under anesthesia (1 minute at 80 cm/H_2O) was 305 ml in the PPS group, versus a mean of 243 ml in the placebo group. The bladder biopsies of all the patients showed features associated with interstitial cystitis syndrome, such as transitional-cell erosion, monuclear infiltrates and mast cells. A moderate to high density of mast cells was observed in seven patients from the PPS group, and in eight from the placebo group. Subjective and objective parameters in the two groups were comparable at the start of the study.

Patients retained the pentosanpolysulfate intravesically for as long as urge and pain made it possible. Retention varied from 30 to almost 180 minutes, without irritative side-effects. Nineteen of the patients managed with self-catheterisation, while one was assisted by a district nurse. Urine cultures remained negative. The main expected side-effect, hematuria, attributed to the heparin-like qualities of the drug, was reported incidentally after instillation. The hematuria always disappeared spontaneously within 2 days, never necessitating a medical consult.

After three months of treatment, an overall subjective improvement in symptoms was reported by four patients (44%) in the PPS group (n=9), by two (20%) in the placebo group (n=10). This difference was not statistically significant. All other patients reported unchanged symptoms. *Table 1* shows the mean values of the objective parameters. Except for the urodynamic capacity other, marginal, differences were not statistically significant. A decrease was noted in the average voiding volume in the PPS-after-placebo group caused by a dramatic decrease in one patient who remained symptomatically unchanged. A statistically significant increase ($p=0.047$, Student t-test, one-tail probe) in the urodynamic capacity was recorded after 3 months of PPS treatment compared to the

pre-trial volume. The increase (from 208 to 229 ml) in the patients receiving PPS after placebo was not statistically significant.

Following the placebo-controlled period of three months eleven (55%) patients continued PPS instillations. Four patients did not continue because they judged their symptoms acceptable while five patients preferred other conservative options. From the group of patients (n=8) who continued with PPS after 3-months-placebo six (75%) reported symptomatic improvement and mean objective parameters improved although, not statistically significant (*Table 1*).

Table 1.

Mean objective parameters pre and post-treatment, determined by micturational profiles and cystometrogram.

	PENTOSAN (n=9)		*PLACEBO* (n=10)		
	Start	3m	Start	3m	6m*
Frequency/24-hrs	18x	18x	22x	24x	19x
Nocturia/24-hrs	4.0x	2.8x	5.0x	5.0x	4.3x
Average volume/24-hrs	116 ml	125 ml	91 ml	107 ml	70 ml
Urodynamic capacity	226 ml	265 ml**	202 ml	208 ml	229 ml
First desire volume	73 ml	74 ml	101 ml	102 ml	67 ml

* = Patients receiving intravesical PPS during 3 months following initial treatment with placebo instillations (n=8).

** = statistically significant increase, p = 0,047

From the 3 patients who continued, following 3-months PPS instillations, 2 reported further impro-

vement and one sustained relief of symptoms. Comparison of short-term and long-term results of PPS instillations was prohibited due to a change in frequency (3 times per week) and composition of the instillations in most of the patients. At one and a half year from the start of the study 8 (40%) of the patients were still receiving PPS instillations; surgical treatment had been applied to 4 (20%) patients, twice after failure of continued PPS instillations and twice after exhausting other conservative options (prolonged hydrodistension under anesthesia, corticosteroids).

DISCUSSION

The primary subjective measurement used to determine effectiveness was the patient evaluation of overall improvement. In the group of patients treated with PPS, 44% experienced symptomatic relief versus 20% of the patients treated with placebo. This difference was not statistically significant. Differences between objective parameters were marginal, only functional bladder capacity showed a statistically significant increase in patients treated with PPS. Eleven (55%) patients continued PPS instillations after completion of the study protocol. One and a half year from the start of the study eight (40%) patients are still on treatment.

The treatment of IC is largely empiric because of the unknown cause of the disease. A wide variety of oral and intravesical agents are currently employed[11]. Employment of pentosanpolysulfate in the treatment of IC is based on the pathogenetic theories referred to previously. The pharmacological effect of PPS is affinity for mucosal membranes, which results in coating of the surface, particularly where the normal sulfonated glycosaminoglycan layer is missing. Furthermore, PPS inhibits inflammatory processes involving lysosomal proteases and inflammatory mediators. Because pentosanpolysulfate orally is absorbed only marginally (3-5%) from the gastro-intestinal tract, we hoped to improve its therapeutic efficacy by intravesical application. The dose we applied was similar to the daily oral prescription (300 mg) and arbitrarily instilled twice a week for a period of 3 months. The double-blind design of the study offered the option of cross-over. However, it was considered inhumane to ask patients with persistent symptoms and pain to risk another three months of only placebo treatment. Reports on oral pentosanpolysulfate have shown moderate to substantial relief of symptoms in 50% up to 80%[4,6]. However, these were un-controlled studies. The main results and characteristics of four placebo-controlled oral PPS studies and our intravesical placebo-controlled PPS trial are shown in *Table 2*[5,7,8,10].

Table 2.

Placebo-contolled studies on pentosanpolysulfate for IC.

	Application	Year	Pts	Drop-outs	age	Relief of Symptoms PPS	Placebo	
Parsons et al.; USA[6]	oral	1987	n=75	17%	-	40%	18%	S
Holm-Bentzen et al.; Europe[7]	oral	1987	n=43	9%	63 yrs	30%	20%	NS
Mulholland et al.; USA[8]	oral	1990	n=110	11%	44 yrs	28%	13%	S
Parsons et al.; USA[9]	oral	1993	n=148	12%	43 yrs	32%	16%	S
Bade et al.; Europe	intravesical	1995	n=20	5%	53 yrs	44%	20%	NS

S = Statistically significant difference ($p<0.05$)

NS = Not statistically significant difference

The oral studies are well compatible in respect of the number of included patients, drop-out percentage and methodology. All of them employed visual analogue scales to evaluate improvement, either subdivided in points (0-5)[7] or in percentages (0-25%-50%-75%-100% improvement)[9] and all studies included patients who failed to respond to prior conservative treatment. However, compared to the placebo-controlled studies from the USA, the European studies lack statistically significance. Our recent epidemiologic study in The Netherlands revealed that general and specific (mast cells) pathological features of bladder biopsies are the mainstays of diagnosis for Dutch urologists[12]. The study of Holm-Bentzen et al. included, in the IC group, only patients with pathologically anatomically verified IC (28 or more mast cells per mm^2). In contrast, the USA studies used

the clinical and endoscopic based NIH criteria to diagnose interstitial cystitis. In addition, one may speculate about a difference in awareness concerning the diagnosis of interstitial cystitis. This suspected transatlantic difference in definition and awareness of IC might well explain for the higher average age and the smaller number of included patients in European studies. Compared to the study of Holm-Bentzen et al. our study demonstrated a similar placebo effect; however, the efficacy of *intravesical* PPS was higher than with oral PPS.

Three additional observations were made on the use of *intravesical* PPS. One (1): All but one of the patients were successfully instructed in self-catheterisation by experienced nurses at the Urology Diagnostic Centre. Self-catheterisation enabled patients to contribute and participate in their own treatment which certainly influenced the psychological impact of the treatment. This is reflected in the low drop-out percentage (5%) compared to oral PPS studies. Two (2): No side-effects were recorded. The duration of medication retention was always determined by the slow exacerbation of symptoms, never by side-effects. This is an advantage of PPS instillations compared to DMSO applications. The garlic halitus of DMSO is well known and irritative symptoms or complications do occur. A controlled study of DMSO in IC (n=30) reported 5 patients with complications from the instillation and in two of them treatment was discontinued[13]. The third (3) and probably most encouraging observation refers to the eleven (55%) patients who decided to continue PPS treatment after termination of the first 3-months-period of the study. At one and a half year from the start of the study eight (40%) patients were still using intravesical PPS. However, in four (20%) patients urinary diversion had been inevitable. This percentage is relatively high and might reflect the severity of symptoms and high number of ’end-stage IC’ in the included IC patients. Even more appreciable is the percentage (40%) of patients still benifiting of intravesical PPS one and a half year from the start of the study. In a study on intravesical heparin (n=48) Parsons et al. reported a long-term remisson with continued treatment in 31% of the patients[14]. However, this was an uncontrolled study. The importance of placebo-controlled studies has well been demonstrated in the studies on oral PPS, and was confirmed by our observation of symptomatic improvement (75%) in the patients who received intravesical PPS after termination of the placebo- and blinded period of the study. Placebo-controlled studies are essential to determine the value of new treatment modalities.

CONCLUSIONS

We concluded the efficacy of *intravesical* PPS to be slight superior to *oral* PPS. In addition, self-

catheterisation enabled long-term treatment and fascilitated the 'self-help' capacity of IC patients. Whether a longer, more intense course of *intravesical* PPS or a combination with other agents will produce better results is currently under investigation.

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CHAPTER 7

A CONTROLLED STUDY ON THE EFFICACY OF INTRAVESICAL OXYBUTININ FOR THE FUNCTIONAL BLADDER CAPACITY OF INTERSTITIAL CYSTITIS PATIENTS

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Submitted

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Abstract:

Objective. To evaluate the extent of activity of intravesical oxybutinin chloride on the low-compliant bladder of interstitial cystitis (IC) patients treated with pentosanpolysulfate (PPS) instillations.

Patients and Methods. Twentytwo IC patients fulfilled the diagnostic NIH-NIADK criteria and received randomly intravesical PPS-oxybutinin and PPS-placebo. Medication was applied thrice a week, with a double-blind cross-over after 6 weeks.

Results. Twenty patients were evaluable. No difference in subjective respons was observed. The patients who applied first PPS-oxybutinin showed a statistically significant change in frequency, average voided volume and maximum voided volume. This was not the case in patients who instilled PPS-oxybutinin during the *second* trial-period of 6 weeks. However, statistically signifant progress of subjective remission was demonstrated in the patients (75%) who persisted PPS-oxybutinin instillations and a further increase of functional capacity.

Conclusions. From the results of this study it would appear that oxybutinin chloride has efficacy ameliorating the symptoms and increasing functional bladder capacity in interstitial cystitis patients. Furthermore, it demonstrated the efficacy and safety of intravesical PPS-oxybutinin for the long-term treatment of interstitial cystitis patients.

INTRODUCTION

Interstitial Cystitis (IC) includes a large group of patients with bladder pain, irritative voiding symptoms (urgency, frequency, nocturia and dysuria) and sterile urine. With little certain about its pathology a committee convened by the National Institutes of Health has arbitrarily proposed a set of characteristics to define the disease[1]. An exponentional growth in clinical and basic research in the past decade did not result in an effective standard treatment for interstitial cystitis.

Surface glycosaminoglycans, the 'mucus' lining of the bladder, have been identified as the defence mechanism coating and protecting the transitional cell surface[2,3]. A current etiologic hypothesis of IC is a defect in the epithelial barrier of the bladder, which allows normal or abnormal substances in the urine to gain inappropiate access to the deeper layers of the bladder wall, initiating a circle of irritation and recruitment of immune cells and immune-mediated responses. Experimentally sodium pentosanpolysulfate (PPS), a heparin analogue, has been shown to reinforce the glycosaminoglycans and reduce transitional cell injury[4]. The pharmacological effect of PPS is affinity for mucosal membranes, which results in coating of the surface, particularly where the normal sulfonated glycosaminoglycan layer is missing. These results and theories formed the rationale to use PPS for the treatment of interstitial cystitis. A number of uncontrolled and placebo-controlled studies has established oral PPS as conservative treatment option for IC[4-9]. Because PPS orally is absorbed only marginally (3-5%) from the gastro-intestinal tract, increased therapeutic efficacy was expected from *intravesical* application of a sulfated polysaccharide[10,11].

Intravesical oxybutinin has been used successfully for the treatment of low-compliant blaaders with small storage capacity[12,13]. Although oxybutinin is more rapidly absorbed into the systemic circulation after intravesical administration than after oral administration, the incidence of systemic side effects has been consistently reported to be low[14,15]. An animal-experimental study did not demonstrate any bladder mucosal changes due to oxybutinin and on the contrary, suggested an protective effect on the mucosa[16].

In the present study we aimed to determine the extent of activity of intravesical oxybutinin chloride on the low-compliant bladder of interstitial cystitis patients treated with pentosanpolysulfate instillations.

PATIENTS AND METHODS

Patients were recruited from the northern part of the Netherlands, with an estimated population of 1.7×10^6; our university hospital serves as a referral hospital. Before institution of treatment,

clinical evaluation comprised routine laboratory examinations, urine culture, urine cytology, a cystometrogram awake (20 cc fill rate per minute) and cystoscopy under anesthesia with coldcup biopsies and anesthetic bladder capacity measurement. Criteria for admission to the trial included symptoms for at least one year, suprapubic or perineal pain relieved partially or totally by voiding and characteristic cystoscopic findings such as petechial bleedingh after distension of the bladder under general anesthesia. Typical histology and mast cells of bladderbiopsies were not mandatory for inclusion. Patients were excluded from participation for age less than 18 years, nocturia less than once, a cystometric bladder capacity of more than 500cc, detrusor hyperreflexia and if they complied with one of the NIH exclusion criteria[1].

Treatment. Prior to installment of therapy patients abstained from any specific IC treatment for a period of at least 4 weeks. Patients received 6 weeks intravesical PPS with placebo and 6 weeks PPS with oxybutinin seperated by a double-blind cross-over. The sequence of the medication was assigned randomly. The code was established and maintained within the pharmaceutical department. Pentosanpolysulfate was ordered commercially (Bayer a.g., München-Germany) as injection fluid vials (100 mg/ml) and oxybutinin chloride (Byk, Zwanenburg, The Netherlands) as crystalline groundsubstance. The hospital pharmacy converted them into sterile bladder instillations of 300 mg PPS in 50 mL saline with or without 10 mg oxybutinin chloride. The solution was colourless, without odour and remained stable for a minimum of 6 weeks, stored in a refrigerator. Prior to installation the solution was warmed up to room temperature. All the patients applied the instillation three times per week and retained the solution for a minimum of 30 minutes. All patients were successfully trained in self-catheterisation.

Evaluation. Efficacy evaluation was based on subjective and objective parameters. Subjective improvement was evaluated using visual analogue scales scoring 0 to 5 points for pain and urge. Improvement was defined as a decrease in the score of at least one value. After two periods of 6 weeks, prior to breaking the code, patients were asked to indicate the most beneficial treatment. The 24-hour frequency, the average voiding volume, the maximum volume voided and the nocturia, all recorded from a 48-hour voiding chart, served as objective parameters. The voiding log was completed by the patient before treatment started and at six-weekly intervals thereafter.

Data analysis. Parameters in each period were analysed between the two groups with the Student t-test for matched pairs for quantitative variables. A one-sided Student t-test was applied because improvement was expected. Qualitative variables, improvement or not, were tested with the Wilcoxon rank test. A ’p value’ smaller than 0.05 was considered to be statistically significant.

RESULTS

Twentytwo consecutively diagnosed IC patients, in accordance with the NIH-NIADK criteria, were enrolled in the study from January ’95 to August ’95. The patients consisted of 21 female and 1 male with an average age of 56.3 years (range 32-80 years). The mean disease history was 6.4 years (range 1-19 years). The average bladder capacity under anesthesia was 378ml (range 220-710 ml) while the average cystometric capacity was 227ml (range 58-500ml). Patients retained the medication intravesically for as long as urge and pain made it possible. Urine cultures remained negative. The main reported side-effect was irritation due to catheterisation. One patient discontinued treatment for this reason and one patient discontinued because of dissatisfaction with the symptomatic treatment effect.

Twenty patients were evaluable. The subjective parameters at the start and after 6 weeks for PPS-placebo instillations and PPS-oxybutinin are shown in *Table 1*. In the second period of 6 weeks similar observations were made in both groups. After the trial period but prior to opening the code 10 patients indicated the PPS-oxybutinin period as the most beneficial treatment period, 3 patients preferred the PPS-placebo period and 7 had no preference.

Table 1

Pre- and post-treatment subjective parameters for the **first** trial-period (6 weeks).

	PPS-PLACEBO (n=10)		PPS-OXYBUTININ (n=10)	
Number of patients who:	Pain	Urge	Pain	Urge
IMPROVED	n=5 (3)	n=4 (3)	n=3 (3)	n=4 (1)
UNCHANGED	n=4 (4)	n=4 (5)	n=7 (2)	n=5 (4)
WORSE	n=1 (3)	n=2 (2)	n=0 (5)	n=1 (2)

( ): Between parentheses the results of the **second** trial-period (6-12 weeks) after cross-over.

Objective parameters were analysed for each period and in each group. *Table 2* presents the

changes in mean micturation frequency, nocturia, average voided volume and maximum voided volume during the *first* trial-period of 6 weeks. In the group of patients treated with PPS-oxybutinin the mean voided volume increased from 135 ±87 ml to 158 ±97 ml and the micturation frequency decreased from 23.5 ±10.8 times per 24 hours to 20.4 ±9.4. Both were statistically significant.

TABLE 2

Pre- and post-treatment mean frequency, nocturia, average voided volume (ml) and maximum voided volume deducted from a 48-hour voiding chart, for the **first** trial-period (6 weeks).

	PPS-PLACEBO (n=10)		PPS-OXYBUTININ (n=10)	
	Start (SD)	6 weeks (SD)	Start (SD)	6 weeks (SD)
Frequency/24-hrs	22.6x (10.0)	20.6x (9.5)	23.5x (10.8)	20.4x (9.4)*****
Nocturia/24-hrs	5.6x (3.1)	4.2x (1.9)*****	4.7x (2.4)	4.1x (2.1)
Average volume per 24 hours	115ml (66)	112ml (59)	135ml (87)	158ml (97)*****
Maximum voided volume/48-hrs	176ml (83)	171ml (84)	211ml (125)	241ml (122)*****

SD = Standard Deviation

* : $p < 0.05$

The same parameters are shown in *Table 3* for the *second* trial-period of 6 weeks. During the second period changes were not statistically significant.

After the double-blind trial period 16 patients elected to continue instillations: 14 patients preferred the PPS-oxybutinin combination, two patients continued intravesical PPS and 4 patients

discontinued the intravesical treatment. To date, 13 patients persisted PPS-oxybutinin instillations more than 3 months post-trial. Parameters at the end of the double blind study period (3 months) were used as baseline for further improvement evaluation. The mean post-trial follow-up was 5.7 months (range 3-11 months). The subjective 'pain' score improved in 11 patients (p=0.017) and remained unchanged in 2; the subjective 'urge' score improved in 11 patients (p=0.017) and remained stable in two. The micturation frequency showed a further decrease from 19.3 ±10.6 times per 24 hours to 16.6 ±10.5. Nocturia improved from a mean 3.9 ±2.8 to 2.4 ±2.1 per night, the mean voided volume increased from a mean 157 ±98 ml to 168 ±80 ml and the maximum recorded (48 hr) voided volume increased from an average of 228 ±165 ml to 299 ±112 ml. These changes in micturational profile were not (yet) statistically significant.

TABLE 3

Pre- and post-treatment mean frequency, nocturia, average voided volume (ml) and maximum voided volume deducted from a 48-hour voiding chart, for the **second** trial-period (6 weeks).

	PPS-PLACEBO (n=10)		PPS-OXYBUTININ (n=10)	
	Start (SD)	6 weeks (SD)	Start (SD)	6 weeks (SD)
Frequency/24-hrs	20.6x (11.4)	20.9x (9.5)	20.4x (11.4)	21.1x (9.4)
Nocturia/24-hrs	4.2x (2.0)	4.1x (1.9)	4.1x (3.0)	4.1x (2.1)
Average volume per 24 hours	112ml (59)	129ml (75)	158ml (97)	152ml (101)
Maximum voided volume/48-hrs	171ml (84)	179ml (101)	241ml (122)	262ml (177)*****

SD = Standard Deviation

* : $p < 0.05$

DISCUSSION

The present study demonstrated a statistical significant increase of the functional bladder capacity during pentosanpolysulfate (PPS) oxybutinin applications in the first period of 6 weeks. The results during the second period were not significant. However, in the patients who persisted PPS-oxybutinin instillations a statistically significant progress of subjective improvement was recorded and in addition, further increase of functional capacity.

The treatment of interstitial cystitis (IC) is largely empiric because of the unknown cause of the disease. The form of treatment most widely applied is probably intravesical pharmacotherapy and a wide variety of intravesical agents are currently employed[17]. Oxybutinin-chloride is a tertiary amine and a weak cholinergic blocker but it is a potent local anesthetic and effective spasmolytic agent in a variety of smooth muscle tissues[18]. Oxybutinin possesses a local anesthetic effect twice that of lidocaine and is considered the most effective anticholinergic[19,20]. Contrary to oxybutinin, PPS has a well recognised efficacy in the treatment of IC patients. In fact, the presence of detrusor hyperreflexia and/or a positive response on oral anticholinergics contradicts the diagnosis interstitial cystitis. Our rationale to use oxybutinin for the treatment of IC consisted of three presumptions. First, we presumed that the anesthetic effect of oxybutinin would enhance the efficacy of PPS. Second, we expected a spasmolytic effect on the usually low-compliant, small capacity bladders. And third, we aimed to bypass the well-known side-effects of anticholinergics by intravesical application.

The mechanism of action of oxybutinin in relaxing bladder muscle is unclear, as is the interaction with PPS. Massad et al. and Madersbacher et al. proposed a direct local detrusor-relaxing effect of oxybutinin[14,15]. PPS has a strong affinity to the glycosaminoglycans mucuslayer of the bladder and might repair leaks[21]. Substantial repair of the glycosaminoglycans layer might have diminished the effect of oxybutinin in the second period. However, this hypothesis is contradicted by the subjective respons, which did not improve in the second period compared to the first. In fact the main subjective response was recorded after 12 weeks, with persistency of applications. A slow favorable subjective response has been reported before after oral PPS intake as well as after intravesical polysulfated polysaccharide treatment[5,8-10]. If the subjective response should be attributed to PPS or to the anesthetic effect of oxybutinin is subject to speculation, at present. However,

- the marked increase in mean voiding volume and subsequently decrease of frequency with persistency of PPS-oxybutin instillations is more likely to be an oxybutinin-related effect. In support of this hypothesis are the data from studies on oral PPS. Mulholland et al. reported a mean increase in

volume per void of 9.8 ml and no changes in frequency between oral PPS and placebo (n=110)[9]. Fritjofsson et al. studied 87 patients and reported an increase in mean volume per void of 7.5 ml and a decrease in frequency of an average 16.5 to 13.0 after 24 weeks of oral PPS treatment[6]. In another controlled study on oral PPS Parsons et al. observed an increase of 17.3 ml in the PPS treated group of patients after 4 months, but no change in frequency[5]. Holm-Bentzen et al. treated 43 European IC patients 4 months with oral PPS or placebo but did not observe any change in frequency of micturation[7]. Intravesical instead of oral application of the polysulfated polysaccharide did not alter the micturational profiles[10]. In an earlier placebo-controlled study (n=20) on intravesical PPS at our institution (*unpublished data*) an increase in mean voided volume of 9 ml was recorded, versus 21 ml in the placebo treated group. In contrast with the minor changes of voiding profiles after PPS treatment, this study showed substantial changes in voiding parameters with PPS-oxybutinin instillations.

Apparently, the significant effect of PPS-oxybutinin in the first period (*Table 2*) was not duplicated in the second (*Table 3*). The first group started instillations after cystoscopy under anesthesia, while the second PPS-oxybutinin group had preceeding PPS-placebo instillations. The difference in start-off conditions between the first and second period hampered the interpretation of pre and post cross-over periods and prohibited compilation of all PPS-oxybutinin treated patients versus all PPS-placebo treated patients. Therefor, we decided to evaluate the two groups of patients per period. The beneficial effect of bladder hydrodistension under anesthesia on IC symptoms is well known. The usually temporarily character of this 'hydrodistension effect' might account for the stabilisation of the results in the second period. It would be of interest to know the long-term results of PPS-oxybutinin versus PPS-placebo. Especially, because persistency of PPS-oxybutinin applications increased the efficacy.

In line with previous reports on intravesical oxybutinin we noted minimal side-effects. None of our patients reported a dry mouth or dizzyness, neither caused retention irritative side-effects other than urge and pain due to delayed micturation. Self-catheterisation caused initially pain in some patients. However, all but one one of the 22 patients managed long-term self-catheterisation. In fact, self-catheterisation and application of medication challenged patients to contribute in their own treatment.

CONCLUSIONS

This study demonstrated the efficacy and safety of intravesical pentosanpolysulfate with oxybutinin

for the treatment of interstitial cystitis patients. It was found that intravesical oxybutinin increased the functional capacity and decreased the frequency of micturation in IC patients. With persistency of PPS-oxybutinin instillations significant relief of symptoms was recorded, while self-catheterisation proved to stimulate the 'self-help' capacities of patients. Both are the main objectives in the treatment of IC as long as an curative treatment is still awaited.

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CHAPTER 8

FAILURE OF SUBSTITUTION CYSTOPLASTY IN THE SURGICAL MANAGEMENT OF INTERSTITIAL CYSTITIS

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Submitted

Read at:

The annual meeting of the Dutch Society for Urology, Veldhoven, The Netherlands, April 1995.

Abstract:

Objective. To evaluate the efficacy of surgical techniques applied to end-stage interstitial cystitis (IC) patients.

Patients and Methods. A retrospective study was performed on all IC patients (n=27) treated at our institution between 1976 and 1992.

Results. Surgical intervention was applied to 13 (45%) IC patients. Only one (14%) out of seven patients experienced complete relief of symptoms after primary (substitution) cystoplasty. In contrast, five (83%) out of six patients had an excellent result following primary urinary diversion, with or without cystectomy. The difference was statistically significant. Neither mast cell density nor cystometric capacity could predict the surgical outcome, only continued contact between urine and the bladder (remnant) proved to be a statistically significant determinant of surgical success.

Conclusions. We recommend primary ileal conduit urinary diversion or a continent urinary reservoir for the surgical treatment of intractable interstitial cystitis.

INTRODUCTION

Interstitial cystitis is a disease state characterised by suprapubic pain, severe urinary urgency, frequency and nocturia. The etiology and pathogenesis of interstitial cystitis is unknown. The diagnosis is based on history, cystoscopy, urodynamic and bladder pathological findings. No specific or typical histo-pathological criteria have been established for interstitial cystitis, despite the frequent association with mast cells. At present, criteria of the National Health Institutes[1] are the main standard for diagnosing interstitial cystitis, but studies which include patients diagnosed before 1987 logically refrain to previously accepted criteria.

If conservative treatment fails in patients who are suffering from severe intractable interstitial cystitis, surgical management is mandatory. A number of surgical alternatives has been proposed, including cystolysis, augmentation cystoplasty, cystectomy with an orthtopic neo-bladder and - supravesical urinary diversion[2]. Unfortunately persisting pain, urgency and frequency, similar to the pre-operative symptoms are well-recognised complications.

To evaluate the effect of different surgical techniques applied to chronic interstitial cystitis patients we analysed the records of 27 interstitial cystitis patients, who formed a consecutive series treated at our hospital between 1976 and 1991.

PATIENTS AND METHODS

A total of 27 interstitial cystitis patients were identified from patient records and theatre reports. Diagnosis was based on the patient's history, cystoscopy result, urodynamic evaluation and the histology of bladder biopsies. Different therapies had been applied, conservative as well as surgical. Patients who underwent surgical treatment were divided in two groups according to the performed technique: the 'Cystoplasty-group' contained patients who underwent primary substitution entero-cystoplasty and the 'Diversion-group' patients after primary supravesical urinary diversion, with or without cystectomy. An 'excellent' surgical result was defined as a situation without any interstitial cystitis symptoms or only very mild symptoms which did not require medical attention. The surgical result was defined as a 'failure' if typical interstitial cystitis symptoms persisted and additional conservative or surgical treatment was required.

Age, the cystometric bladder capacity (deduced from urodynamic investigations), histopathology, mastocytosis, disease history prior to surgery of all patients were determined to detect possible predictors for the outcome of surgery.

Fisher's exact test for categorical variables was used to detect significant differences between the

two surgery groups.

RESULTS

Between 1976 and 1992, 27 interstitial cystitis patients were treated. The group comprised 23 females and 4 males, with an average age of 55.5 (25-73) years at the time of diagnosis. The average follow-up period of surgical patients was 11 years, range 3 to 18 years. Conservative treatment modalities included: antibiotics, corticosteroids, heparine injections, oxychlorosene sodium and intravesical DMSO or mytomicine-C, transurethral fulguration of the affected areas, prolonged hydrodistension of the bladder (Helmstein), micturation behavioural training and peroxi-norm submucosal injections. The first choice of treatment changed over the years. In 14 (55%) patients relief of symptoms was achieved with conservative treatment. Nine different drugs or modalities had been recorded as the final ("successful") treatment; only prolonged bladderhydrodistension (Helmstein) had been recorded in three patients. Failure of conservative treatment led to surgical intervention in 13 (45%) patients. Characteristics of these patients (n=13) are shown in *Table I.*

The ’Cystoplasty-group’ consisted of 7 patients with an average age at the time of operation of 44.6 years, a mean cystometric bladder capacity of 265 ml and typical interstitial cystitis histopathological features, including mastocytosis, in all patients. The disease history and duration of treatment prior to surgery mounted 4.0 years (range 2 - 7 yrs). Surgical techniques applied in the ’Cystoplasty-group’ were supra-trigonal cystectomy with ileocystoplasty (n=4), ileocystoplasty (n=2) and sigmoideocystoplasty (n=1). In one patient, the result was excellent (no. 10, table 1), while in six patients the augmentation cystoplasty failed. Three patients refused any further surgery and in three a second surgical intervention was performed, after 13 to 63 months, with success. The second procedure consisted of a supravesical urinary diversion with total cystectomy (no.8, 12 *Table I*) and in one patient a third intervention followed failure of a Mainz pouch (no.7 *Table I*).

The ’Diversion-group’ consisted of 6 patients with an average age at the time of operation of 67.6 years, a mean cystometric bladder capacity of 320 ml and typical interstitial cystitis histopathological features in all patients. But mastocytosis was observed in only 3 patients. The disease history and duration of treatment prior to surgery mounted 7.3 years (range 5 - 15 yrs). Primary surgery in this group consisted of uretero-ileo-cutaneostomy (ileal conduit) with total cystectomy (n=3), uretero-ileo-cutaneostomy only (n=2) and uretero-sigmoideo-cutaneostomy (n=1). In all but one patient, the results were excellent. Subtotal cystectomy was performed after 8 months on the patient in whom surgery had failed (no. 11, *Table I*), followed by total cystectomy and urethrecto-

my after 12 months.

The difference in surgical results between both groups was statistically significant, p = 0.0251 (Fisher's exact test).

DISCUSSION

Between 1976 and 1992, 27 consecutive interstitial cystitis patients were treated. Surgery was used in 13 (48%) of them. Long-term follow-up showed that primary urinary diversion resulted in a success rate of 83% while the success rate of primary (substitution) enterocystoplasty was 14%. The difference was statistically significant.

All the patients were diagnosed according to generally accepted criteria at that time. Mastocytosis and histopathology of bladderbiopsies were mainstays of the diagnosis. Retrospectively, they were all found to fullfil the National Health Criteria of the USA[1]. Conservative treatment had been applied first using 13 different modalities. A sustained symptomatic remission was achieved in 14 patients following a wide variety of "final" treatments. Only prolonged hydrodistension (Helmstein) resulted more than once in a sustained relief of symptoms. The multitude of therapeutic approaches demonstrates that none were significantly superior to the others.

A total of 13 patients (45%) subsequently underwent surgery. This is higher than reported estimates of 10% to 30%[2,3]. The average interval of 4 years ('cystoplasty-group') to 7.3 years ('diversion-group') between diagnosis and surgery, suggests reluctance rather than preference of surgical intervention. Several circumstances might have contributed to the relatively high number of end-stage IC patients at our institution. First, this hospital serves as a second and third referral hospital for a large area. Second, the importance of histopathological features for the diagnosis of IC and third, a transatlantic difference in awareness for IC might have resulted in a selected group of IC patients[4].

The therapeutic success of urinary diversion in IC patients has long been recognised[5]. However, usually the patient's preference and the doctor's aim are to prevent an abdominal stoma and to maintain an intact urinary tract. There was no standard policy at our institution. Apparently, urinary diversion was preferred in elder patients while substitution or augmentation enterocystoplasty was mainly performed in younger patients. Success rates between 84% and 100% have been reported in studies from the USA on enterocystoplasty for the management of IC [6-8]. In contrast, European studies reported lower success rates between 25% to 62%[8-11]. In this study only one patient (14%) was free of symptoms following ileocystoplasty. An explanation is not easy at hand. The reason for

surgical failure of enterocystoplasty is not known[12,13]. An explanatory hypothesis might be found in the crucial role of urine in these patients. The presence of toxic agents in urine is one of the proposed etiologies of interstitial cystitis[10]. It is possible that substitution cystoplasty or augmentation cystoplasty failed because of continued interaction between the remnant bladder tissue and urine. In the vast majority of our surgical patients, success or failure could be related to continued or discontinued contact between urine and bladder tissue. The difference was statistically significant. Only one patient (no. 10, *Table I*) showed complete relief after augmentation cystoplasty, while one patient suffered from continued pelvic pain and urgency after supravesical diversion (no. 11, *Table I*). Total cystectomy and finally urethrectomy did not relieve her pain completely. But, of course other factors e.g. neurological and/or cerebral may also influence the symptoms, as has been suggested previously[14]. Reducing the bladder remnant to prevent 'failure' has been advocated. However, the extension of subtotal cystectomy with disconnection of the ureters from the trigone and reimplantation into the enterocystoplasty, did not prevent failure[15].

Several authors studied possible predictors of the outcome from augmentation cystoplasty. Nielsen et al. did not detect a correlation between the outcome of supratrigonal cystectomy and mast cell density or trigone histology[11]. Pre-operative bladder capacity under anaesthesia has been suggested as predictor. Failure of substitution cystoplasty was reported in IC patients with functional bladder capacity above 350 ml and above 250 ml[8,16]. In our study mast cell counts and histopathology of bladder biopsies did not differ significantly between both groups. Reliable data on the bladder capacity under anaesthesia were not available. In four patients (no. 4, 7, 9, 10 *Table I*) of the 'cystoplasty-group' a cystometric capacity below 250 ml was measured. However, only one had an excellent outcome of surgery. In this study cystometric bladder capacity did not have any value regarding the outcome of surgical treatment.

If symptoms persist, the bladder (remnant) is held responsible and total cystectomy with supravesical diversion is performed as a panacea to, finally, relieve the patient's complaints. However, it has been recognised since 1978 that supravesical diversion without cystectomy can lead to total symptomatic relief of interstitial cystitis symptoms[5]. This has been confirmed in a report on the fate of 30 bladders after urinary diversion, among them three bladders of interstitial cystitis patients[17]. Also in this study 3 patients (no. 1,6 and 11 *Table I*) had an excellent outcome after urine diversion only. If our hypothesis that the combination of the bladder and urine is essential in creating typical interstitial cystitis symptoms is true, failure of (substitution) cystoplasty in an IC patient should not necessarily lead to total cystectomy. Urinary diversion alone will be adequate

and the advantage of reduced morbidity is obvious. Alternatives for a conduit urinary diversion are a continent pouch or total substitution of the lower urinary tract. Five successfully treated patients with total substitution have been reported[4]. However, IC symptoms and pain developing in continent diversions make one cautious about this form of diversion[12].

CONCLUSIONS

In this study discontinuation of urine - bladder contact proved to be essential in determining the success or failure of surgical treatment for interstitial cystitis patients. The outcome of (substitution) cystoplasty was very poor. We recommend primary ileal conduit urinary diversion or a continent urinary reservoir for the surgical treatment of intractable interstitial cystitis. There is no rationale to combine urinary diversion with a (sub)total cystectomy as a first surgical step (unless total bladder replacement is performed).

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Table I.

Characteristics of interstitial cystitis patients treated surgically (n=13), 1976-1991.

No	age-/sex	functional capacity	masocytosis	type of surgery	year of surgery	outcome	next treatment
1	59-F	120 ml	-	Coffey's urine diversion	1976	excellent	-
2	68-M	90 ml	-	subtotal cystectomy + ileal conduit	1978	excellent	-
3	70-F	400 ml	-	total cystectomy + ileal conduit	1980	excellent	-
4	32-F	160 ml	+	subtotal cystectomy + ileocystoplasty	1980	poor	conservative
5	75-F	450 ml	+	total cystectomy + ileal conduit	1980	excellent	-
6	82-F	?	+	ileal conduit	1982	excellent	-
7	29-F	150 ml	+	sigmoideocystoplasty	1982	poor	63m.:Mainz pouch; 76m.:ileal conduit.
8	45-F	395 ml	+	subtotal cystectomy + ileocystoplasty	1985	poor	13 m.: total cyst. + ileal conduit
9	25-F	170 ml	+	subtotal cystectomy + ileocystoplasty	1988	poor	conservative
10	60-F	100 ml	+	ileocystoplasty	1989	excellent	-
11	52-F	540 ml	+	ileal conduit	1989	poor	12m.:subtot. cystectomy; 24m.: total cyst. with urethrec-tomy
12	58-M	480 ml	+	subtotal cystectomy + ileocystoplasty	1991	poor	36 m.: total cyst. + ileal conduit
13	63-F	400 ml	+	ileocystoplasty	1992	poor	conservative

CHAPTER 9

IS THERE A RATIONALE FOR DIETARY GUIDELINES IN INTERSTITIAL CYSTITIS?

BADE JJ, PEETERS JMC, MENSINK HJA

Submitted

Abstract:

Objective: To evaluate the consumption of foods and fluids from interstitial cystitis (IC) patients compared to the averages of the general population, and to investigate any spontaneous preference or avoidance of specific foods and liquids among interstitial cystitis patients.

Patients and Methods A descriptive study. A verbal interview of 16 IC patients provided information on consumption of foods and fluids as well as dietary habits. The results were compared with averages of the general population. The one-sample Student t-test and the Chi-square test were used to detect statistically significance.

Results IC patients consumed statistically significant less energy, fat and coffee, and statistically significant more fibres and tea than the general population. The intake of other acid-producing- foods did not differ from the general population. All the IC patients, prior to the dietary interview, were unaware of any possible dietary measures in relation to their IC symptoms.

Conclusion According to general standards the 16 IC patients had a more healthy daily diet compared to the general population. The IC patients consumed statistical significant less coffee (caffeine) compared to the general population. This confirms previous reports on studies demonstrating an excerbation of irritative IC symptoms following caffeine provocation. A caffeine-restricted diet for symptomatic IC patients is the single dietary advise supported by the data of this study.

INTRODUCTION

Interstitial Cystitis (IC), as part of the painful bladder disease complex, includes a large group of patients with bladder pain, irritative voiding symptoms (frequency, urgency, nocturia and dysuria) and sterile urine. Interstitial cystitis remains essentially a diagnosis of exclusion, with little certain about its etiology and little distinctive about its pathology[1,2]. A committee convened by the National Institutes of Health (U.S.A.) has arbitrarily proposed a set of characteristics to define the disease[3]. A large number of treatment modalities are currently being employed[4]. Often, dietary advice forms part of the therapeutic approach to IC patients, with the aim of influencing the irritative symptomatic expression of the disease. Besides the wide variety of dietary advice from concerned neighbours and relatives, more uniform and specific dietary guidelines are given by doctors and information bulletins from the ICA (Interstitial Cystitis Association, a non-profit health organisation that provides support for IC patients in the United States). Food products considered to exacerbate irritative symptoms include caffeine, citrus fruits, wine and other alcoholic drinks, chocolate, yogurt, sour cream and bananas[5,6]. The rationale of such dietary advice is largely anecdotical in nature and although some patients may benefit, others may experience it as restricting their quality of life. In the Netherlands, a supportive IC patient association and structural (dietary) information on interstitial cystitis are absent.

In a prospective study, we evaluated the dietary habits of interstitial cystitis patients and compared them to the average diet of the general population. We also investigated whether there was any spontaneous preference or avoidance of specific foodstuffs and fluids by IC patients.

PATIENTS AND METHODS

Symptomatic interstitial cystitis patients were selected for dietary evaluation. All patients were admitted for diagnostic evaluation including routine laboratory examinations, urine culture, urine cytology, a cystometrogram awake (20 cc fill rate per minute) and cystoscopy under anaesthesia with coldcup biopsies and capacity measurement (1 minute at 80 cm H_2O pressure). In addition, the weight of each patient was recorded and their renal function and 24-hour urine pH were measured. During admission all patients were verbally and in written interviewed by one dietician. The study had three parts. In the *first part*, the dietary daily intake was quantified for each patient, including energy, foodconstituents, fluids and specific foods. The results were compared to the average intake of the general population, corrected for age and gender[7]. A map with figures of cups, glasses and meals (plates) was used as reference to quantify the intake of food and liquids[8]. In the *second part* acid-urine-producing and symptom-provocating foods (based on the publications of the interstitial cystitis association in the United States) were listed. Consumption of each

specific food was scored with yes or no. The list included coca-cola, carbonated soft drinks, sour milk products, grapes, grape juice, coffee, tea, citrus fruits, tomatoes, vinegar, spicy foods, alcoholic beverages, chocolate and artificial sweeteners. The *third part* contained open questions about the tolerance of specific foods, fluids and food supplements, and whether the patients had received any previous dietary information or instructions.

Data analysis. To determine the statistical significance of any differences in consumption between the interstitial cystitis patients and the general population we used the two sided Student t-test. The Chi-square test was applied to the differences in actual consumer numbers between the two groups with regard to specific foods. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 16 consecutively diagnosed interstitial cystitis patients were interviewed in the period May '94 to October '94. All the patients were female, the mean age was 51.5 years (range 24 - 80 years), the mean disease history was 4.6 years (range 1.5 to 18 years) and the average weight was 71.1 kg (range 52 - 90 kg). According to the weight-height curves for female adults, the weight of one patient was above the 90 percentile line, while the others were between the 10^{th} and 90^{th} percentiles. The pH was measured in 24-hour urine. Two urine samples had a pH of 5.0, three a pH of 6.0 and 14 a pH of 7.0. The renal function, expressed as creatinine clearance (ml per min) of all the patients was normal.

Part 1. The daily food intake of the interstitial cystitis patients compared to the general population is shown in *Table 1*. The mean daily energy intake in the IC group was significantly less ($p<0.05$) than in the general population. In addition, a significantly reduced intake of fat ($p<0.01$) and an increased intake of fibres ($p<0.01$) was recorded. T*able 2* shows the daily intake of specific fluids. The majority of IC patients did not consume coca cola, grapefruit or orange juice. Only the mean daily tea consumption of the IC patients was significantly higher ($p<0.01$). T*able 3* compares the average daily consumption of specific food products. Consumption of staple foods did not differ significantly, except for meat and meat products ($p<0.05$). The IC patients consumed significantly less cake and biscuits ($p<0.01$), and less nuts ($p<0.01$) than the general population.

Table 1

Average daily intake of energy (Kj and kcal), food constituents (g) and water (ml). Interstitial cystitis patients were compared to the general population, corrected for age and gender.

	IC Patients	SD	General Pop.	Difference
Energy:				
Kj/day	7,046	(1,604)	8,078	-1,032 S
Kcal/day	1,677	(301)	1,930	-253 S
Water (ml/day)	2,639	(810)	2,267	+372
Protein (g/day)	66	(19)	76	-10
Fat (g/day)	65	(17)	82	-17 S*
Carbohydrates (g/day)	207	(48)	209	-2
Fibres (g/day)	22	(8)	15	+7 S*
Vitamin C (mg/day)*	108	(55)	80	+28

* = tablets were not included

S = Significant, $p < 0.05$ S*= Significant, $p< 0.01$

SD = Standard Deviation

Table 2

Average daily intake of specific fluids (ml) by interstitial cystitis patients compared to the general population, corrected for age and gender.

	IC Patients	SD	General Pop.	Difference
Tea (n=16)	717	(422)	380	+337 S*
Coffee (n=11)	379	(390)	540	-161
Sour dairy prod.(n=13)	192	(282)	116	+76
Carbonated soft drinks (n=8)	135	(173)	64	+71
Coca cola (n=4)	71	(151)	20	+51
Orange juice (n=5)	16	(315)	36	-20
Grapefruit juice (n=3)	3		2	+1

S* = Significant, $p < 0.01$

(n)= Between brackets the actual number of consumers among the IC patients

SD = Standard Deviation

Part 2. The number (percentages) of IC patients who consumed acid-urine-producing or symptom-provocating foods are shown in *table 4*. There were significantly fewer coffee consumers ($p<0.01$) and significantly more tea consumers ($p<0.05$). The difference in orange juice consumers was not significant.

Table 3

Average intake of specific foodstuffs (g) per day by interstitial cystitis patients compared to the general population, corrected for age and gender.

	IC Patients	General Pop.	Difference	
Potatoes	87	107	-20	
Bread	130	117	-13	
Vegetables	162	144	+17	
Meat and meat products	86	105	-18	S
Cereals	32	36	-4	
Cake and biscuits	26	48	-22	S*
Sugar and sweets	48	30	+18	
Nuts	9	20	-11	S*
Soup	53	73	-20	
Fat and sauces	36	41	-5	
Cheese	34	29	+5	
Eggs	8	14	-6	
Fish	7	10	-3	
Beans	8	6	+2	
Fruits	174	138	+36	

S = Significant, $p < 0.05$

S* = Significant, $p < 0.01$

Table 4

The actual number of interstitial cystitis patients who consumed acid-urine-producing foods.

	I.C. patients	General population	
Coca-cola	n=4 (25%)	7.5%	
Carbonated soft drinks	n=8 (50%)	*	
Sour milk poducts	n=13 (81%)	*	
Grapes	n=4 (25%)	6.6%	
Grape juice	n=3 (19%)	1.3%	
Coffee	n=11 (68%)	92.3%	S*
Tea	n=16 (100%)	79.2%	S
Oranges juice	n=5 (31%)	26.6%	
Citrus fruit	n=9 (56%)	*	
Tomatoes	n=10 (63%)	*	
Vinegar	n=9 (56%)	*	
Spicy foods	n=6 (38%)	*	
Alcohol liquids	n=6 (38%)	*	
Chocolate	n=3 (19%)	*	
Artificial sweeteners	n=3 (19%)	*	

S = Significant, $p < 0.05$
S* = Significant, $p < 0.01$
* = No data available of this subgroup for the general population.

Part 3. None of the IC patients had ever received information or instructions about dietary management of their IC symptoms. Only two interstitial cystitis patients experienced an exacerbation of symptoms in relation to consuming specific foods or fluids. One patient reported a coincidence of symptom relapse and a high intake of orange and lemon juice (2.5 l/day) and another patient reported a similar coincidence after drinking coffee. In a period of excessive symptoms six patients deliberately increased their fluid intake, five lowered it and five did not change it.

DISCUSSION

In this study IC patients consumed statistically significantly less calories and fat ($p<0.05$), and statistically significantly more fibres ($p<0.05$) than the general population. In addition, a statistically significantly lower consumption of cake - biscuits ($p<0.01$) and nuts ($p<0.01$) was demonstrated. Furthermore, among IC patients were significantly fewer coffee consumers ($p<0.01$) and significantly more tea consumers ($p<0.05$). The difference in orange juice consumers was not significant.

A causative relation between diet and disease is well-recognised for a number of foodsubstances and organs, e.g. cholesterol and heart failure and suggested for others. The significant differences in the incidence of prostate cancer between the "Far East" and "Western countries" have been related to different diets and a ’causative’ or ’protective’ influence of fatty or fibre food constituents was suggested, although the explanatory theories are largely hypothetical[9]. In a, questionnaire-based, dietary study Bitterman et al found a correlation between the quantity of fluid intake and the prevalence of urologic cancers[10]. It is not yet clear whether there is a relation between diet and interstitial cystitis. In the United States almost all IC patients are given advice about dietary measures to influence their interstitial cystitis symptoms, whereas in the Netherlands, no structural information is available for IC patients. A urologist-based questionnaire, conducted in 1994, revealed that 66% of Dutch urologists never and 34% occasionaly use dietary advise in the treatment of interstitial cystitis[11].

None of the participants in our study had received any specific information or instructions regarding their diet in relation to their symptoms prior to the study. The general population statistics were corrected for weight and height, age and gender to make them compatible with IC patients. Except for their interstitial cystitis syndrome our patients were healthy with normal renal function and urine pH. The consumption of significantly less energy, fat, cakes & biscuits and nuts, and more fibres is generally considered to be healthy. The interpretation of this finding is rather speculative. Three explanations are possible: firtstly, the ’healthier’ diet of IC patients reflects mechanisms secondary to the chronic disease, i.e. the intention to follow the most healthy life-style possible in order to reduce the severity of the symptoms, secondly, it might result from the loss of appetite due to debilitating symptoms and thirdly, it reflects cautious compliance with the advice of non-medical acquaintances who often advise extra fruit, vegetables or specific herbal teas. Which theory is applicable remains unclear, but the interstitial cystitis syndrome was the only difference in condition compared to the healthy individuals of the ’general population’ and therefore, most probably responsible for the statistically significant differences in diet.

Whitmore et al combined 3-day food and voiding diaries with a quality-of-life questionnaire and demonstrated that the ingestion of acid-urine-producing foods or fluids was associated with an increase in

painful bladder symptoms, while the elimination of acid-urine-producing foods and fluids resulted in the diminution of symptoms[6]. Koziol et al reported that 50% of interstitial cystitis patients identified acid-urine-producing foods or fluids as being the cause for a flare in pain[12]. Gillespie reported a marked reduction in pain and frequency in 10 interstitial cystitis patients after dietary restriction of acid-urine-producing foods and foods high in tyrosine, tyramine, asparatate and phenylalanine. Re-challenge with these foodstuffs triggered the onset of symptoms[13]. Presumably, if a specific food or fluid has a clear irritative or protective effect on the intensity of the symptoms, a spontaneous deliberate preference or avoidance of these foodstuffs might follow. In our study, with severe symptomatic IC patients, we observed significantly more tea consumers and fewer coffee consumers. However, the difference in the average intake of coffee was not statistically significant ($p=0.065$) due to the wide variation (Tables 2 and 4). This finding, more tea and less coffee consumption, seems to be contradictory because both fluids contain caffeine, but tea contains far less (40 mg per 150 ml) than coffee (115 mg per 150 ml). Furthermore, although it was not included as a specific question, most of the patients reported a preference for herbal teas, most of which are caffeine-free. Also coca cola (20 mg caffeine per 150 ml) and chocolate (100 mg per 150 ml) consumption were low (Table 4). Thus, our observation of a spontaneous reduction in caffeine intake by non-informed IC patients suggests a relation between IC symptoms and caffeine. This confirms the results of the aforementioned studies. The exact metabolic connection between caffeine and painful bladder symptoms is not known. In general, caffeine is known to have a stimulative effect on the central nervous system due to competitive antagonism with adenosin receptors. Increased diuresis is one of the effects. The increased speed of bladder filling may exacerbate the symptoms. In contrast, six patients deliberately increased their fluid intake during the exacerbation of symptoms in order to obtain more relief from micturation or to benifit from less concentrated urine. With regard to other acid-urine-producing foods, no decrease was observed but a slight increase was noted.

CONCLUSIONS

Although dietary management seems to offer a cost-effective approach to IC patients and to stimulate the "self-help" regimes for IC patients, it might also restrict their quality of life. Until controlled, single-blind, restriction-provocation studies on the effect of different foodstuffs have been performed, strict dietary manipulation is not justified in IC patients at present. The data of this study support the notion that a caffeine-restrictive diet might reduce irritative interstitial cystitis symptoms. No rationale for other dietary manipulation was found.

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CHAPTER 10.

SUMMARY AND CONCLUSIONS

Little has been added during the last 80 years to the astute recognition by Hunner of advanced cases of interstitial cystitis as "a rare type of bladder ulcer". This thesis is an attempt to solve the question as to what triggers the disease. Is it autoimmunity? And is there a conservative treatment with superior benefit for interstitial cystitis patients?

The epidemiology of interstitial cystitis has always tantalized urologists. In **CHAPTER 2** the results are discussed of a urologist-based epidemiologic study. The prevalence of interstitial cystitis in the Netherlands is estimated at 8 to 16 cases per 100,000 female adults, which probably is a conservative estimate since only interstitial cystitis patients who sought treatment were reported. Mast cells had an important role in the diagnosis of interstitial cystitis and were reported by 80% of the Dutch urologists as a diagnostic criterion. Difference in definition and awareness of interstitial cystitis could explain the difference in prevalence of interstitial cystitis. Dimethyl Sulfoxide instillations and hydrodistension of the bladder were practised by more then 80% of the Dutch urologists. This fairly uniform therapy preference demonstrates a remarkable consensus among Dutch urologists concerning interstitial cystitis.

In 1950 two virologists, Tamm and Horsfall, discovered a glycoprotein that now bears their names. Tamm-Horsfall Protein (THP) is the most abundant protein in normal urine and a major component of tubular and urinary casts. THP is synthesized exclusively in the kidney. Several pathophysiological actions have been suggested. For instance, (1) THP was found to bind to E. Coli bacteria which should prevent the adhesion of bacteria to the urinary epithelium; (2) THP seems to be a constant component of renal stones; and (3) interstitial nephropathy was demonstrated in experimental rat and rabbit models after active immunisation with THP. In addition, intraurothelial THP and elevated levels of antibody to THP demonstrated in IC patients seem to confirm the theory of increased bladder permeability to urinary constituents as the etiological mechanism of IC and to offer a possible diagnostic marker. In **CHAPTER 3** the results are presented of a prospective study on urinary Tamm-Horsfall protein (THP) excretion. A significant difference was detected between (female) interstitial cystitis patients (n=28) and (female) controls (n=25). Despite the increased values, no Tamm-Horsfall protein bladder depositions could be demonstrated. The increased urinary THP levels in interstitial cystitis patients support the etiological theory of a systemic disease.

In further support for a systemic etiologic pathogenesis are the many facets of interstitial cystitis similar

to well-known auto-immune diseases. Firstly, 90% of the patients is female, with a preferential age between 20 and 60 years. Secondly, the episodic waxing and waning of the disease. Thirdly, the onset of disease is often well memorised by patients even after many years, which indicates a subacute onset. Fourth, histopathological examination of the bladder wall shows the localised presence of dense mononuclear infiltrates in which lymfocytes are abundantly present. The demonstration of mast cells is characteristic in these biopsies. Fifth, a considerable number of IC patients has been co-diagnosed with well-known auto-immune diseases, i.e. lupus erythematosis, polyarteritis nodosa, rheumatoid arthritis, ulcerative colitis and M. Sjogren. In **CHAPTER 4** a study was was designed to evaluate the presence of tissue-specific auto-antibodies in IC patients using a direct immunostaining technique not reported before in relation with IC patients. We demonstrated the presence of specific auto-antibodies in all (n=3) tested IC patients. The auto-antibodies were directed against epithelium and muscle fibers of the bladder wall. Bladder tissue treated with control serum showed no response. In two out of the three patients Antinuclear antibodies (ANA) were demonstrated. The findings in this study provide new evidence for an auto-immune involvement in interstitial cystitis. Whether the interpretation of this finding hint at a primary or a secundary auto-immune pathogenesis is rather speculative, presently. Nevertheless, the specific auto-antibodies demonstrated call for a reappraisal of a systemic autoimmune pathogenesis in interstitial cystitis and hence, for reconsideration of immunosuppressiva and corticosteroids in the treatment of interstitial cystitis.

Traditional, therapy for interstitial cystitis has been clinically and scientifically unsatisfactory. Many regimens have been heralded in preliminary reports, only to be abandoned within several years. Surface glycosaminoglycans, the ’mucus’ lining of the bladder, have been identified as the defence mechanism coating and protecting the transitional cell surface. Experimentally sodium pentosanpolysulfate, a heparin analogue, has been shown to reinforce the glycosaminoglycans and reduce transitional cell injury. These results and theories formed the rationale for use of pentosanpolysulfate in the treatment of interstitial cystitis. However, studies on oral pentosanpolysulfate reported various success rates. We attempted (**CHAPTER 5**) to improve the oral therapeutic results by intravesical application (two times a week) of pentosanpolysulfate, and to observe tolerance and side effects. In a pre-liminary study we observed long-term symptomatic relief and objective improvement in four out of six patients. The tolerance of intravesical pentosanpolysulfate was excellent and in addition, prolonged treatment reduced frequency of cyclic relapses.

Based on the results of the pilot study, a placebo-controlled prospective, double-blind study was designed (**CHAPTER 6**) to evaluate the therapeutic efficacy of intravesical pentosanpolysulfate (PPS) compared to placebo in IC patients. A total of 20 consecutively diagnosed patients were enrolled in the

study from May ’94 to December ’94. All the patients were women, with an average age of 53.8 years (range 24 - 75 years) in the pentosanpolysulfate group versus 52.8 years (range 24 - 79) years in the placebo group. Patients applied *intravesical* PPS *twice* in a week, either by selfcatheterisation or with the help of a district nurse. In the group of patients treated with PPS 40% experienced symptomatic relief versus 20% of the patients treated with placebo. This difference was not statistically significant. Differences between objective parameters were marginal, only functional bladder capacity showed a statistically significant increase in patients treated with pentosanpolysulfate. Eleven (55%) patients continued PPS instillations after completion of the study protocol.

In **CHAPTER 7** the results are presented of a more intense course (instillations *three* times per week) with *intravesical* PPS-placebo and PPS-oxybutinin. A total of 22 consecutively diagnosed interstitial cystitis patients participated in the study from February ’95 to December ’95. Twenty patients were evaluable. The subjective parameters in the *first* and the *second* period did not differ between the patients treated with PPS-placebo instillations and patients instilled with PPS-oxybutinin. In the group of patients treated with PPS-oxybutinin, in the *first* period, the mean voided volume increased from 135 ±87 ml to 158 ±97 ml and the micturation frequency decreased from 23.5 ±10.8 times per 24 hours to 20.4 ±9.4. Both were statistically significant. During the second period changes were not statistically significant. However, after the double-blind trial period 14 (75%) patients elected to continue PPS-oxybutinin instillations. The mean post-trial follow-up was 5.7 months (range 3-11 months). The subjective ’pain’ score improved in 11 patients (p=0.017) and remained unchanged in 2; the subjective ’urge’ score improved in 11 patients (p=0.017) and remained stable in two patients. The micturation frequency showed a further decrease from 19.3 ±10.6 times per 24 hours to 16.6 ±10.5. Nocturia improved from a mean 3.9 ±2.8 to 2.4 ±2.1 per night, the mean voided volume increased from a mean 157 ±98 ml to 168 ±80 ml and the maximum recorded (48 hr) voided volume increased from an average of 228 ±165 ml to 299 ±112 ml. These changes in micturational profile were not (yet) statistically significant. From the results of this study it would appear that oxybutinin chloride has efficacy ameliorating the symptoms and increasing functional bladder capacity in interstitial cystitis patients. Furthermore, it demonstrated the efficacy and safety of intravesical PPS-oxybutinin for the long-term treatment of interstitial cystitis patients.

However, if conservative treatment fails in patients who are suffering from severe intractable interstitial cystitis, surgical management is mandatory. A number of surgical alternatives have been proposed, including cystolysis, subtotal cystectomy with substitution cystoplasty and total cystourethrectomy with supravesical urinary diversion. Unfortunately persisting pain, urgency and frequency, similar to the preoperative symptoms are well-recognised complications. The records of 27 interstitial cystitis patients, who

formed a consecutive series treated at our hospital between 1976 and 1991, were analysed. The results are presented in **CHAPTER 8**. Surgery was used in 45% of them. Long-term follow-up showed that urinary diversion was significantly superior to non-diversion vesical surgery ($p<0.05$). Our data demonstrate that urinary diversion, i.e. discontinuation of urine-bladder contact, proved to be essential in determining the success or failure of surgical treatment for interstitial cystitis patients. The consequence should be a surgical policy, after the conservative options have been exhausted, comprising primary supravesical diversion without cystectomy or total cystectomy with an orthotopic neobladder.

Usually dietary manipulation is part of the treatment of interstitial cystitis patients in the USA. Our urologist-based questionnaire revealed that only 34% of Dutch urologists occasionaly use dietary advise in the treatment of interstitial cystitis. In a prospective study, presented in **CHAPTER 9**, we evaluated the dietary habits of interstitial cystitis patients. The interstitial cystitis patients consumed statistically significantly less calories and fat ($p<0.05$), and statistically significantly more fibres ($p<0.05$) than the general population. In addition, a statistically significantly lower consumption of cake-biscuits ($p<0.01$) and nuts ($p<0.01$) was demonstrated. Furthermore, among IC patients were significantly fewer coffee consumers ($p<0.01$) and significantly more tea consumers ($p<0.05$). The difference in orange juice consumers was not significant. In conclusion, although dietary management seems to offer a cost-effective approach to IC patients and to stimulate the "self-help" regimes for IC patients, it might also restrict their quality of life. Strict dietary manipulation is not justified in IC patients at present. The data of this study support the notion that a caffeine-restrictive diet might reduce irritative interstitial cystitis symptoms. No rationale for other dietary manipulation was found.

It is my hope that this thesis will stimulate awareness, recognition and research in interstitial cystitis in The Netherlands, and might serve as a guideline for urologists in the treatment of interstitial cystitis patients

Samenvatting

Hoofdstuk 1

De klachten van patiënten met het *blaaspijnsyndroom, cystitis interstitialis (CI)*, worden al meer dan tachtig jaar gedetailleerd beschreven. In al die jaren is het de medische wetenschap niet gelukt dichter bij de oorzaak of genezing van de kwaal te komen. In de Verenigde Staten bestaat sinds 1985 een patiëntenvereniging die in belangrijke mate heeft bijgedragen aan de exponentiële groei van het onderzoek naar CI. De kosten voor CI-research stijgen daar dan ook naar verhouding reuze snel!

Nederland kent geen patiëntenvereniging en CI is, de urologen uitgezonderd, hier vrijwel onbekend. De dramatiek van het ziektebeeld en het ontbreken van een adequate standaardtherapie vormen echter voldoende reden voor nader onderzoek.

Hoofdstuk 2 *beschrijft de Nederlandse situatie: het aantal CI-patiënten, gepraktizeerde diagnostiek en therapie.*
De mogelijke oorzaak van CI en een eventuele diagnostische test worden in de **hoofdstukken 3 en 4** *belicht.*
Vanaf hoofdstuk 5 wordt onderzoek naar een meer effectieve behandeling beschreven. Na een verkennende studie (**hoofdstuk 5**) *wordt pentosanpolysulfaat vergeleken met placebo* (**hoofdstuk 6**). *Optimalisering van de behandeling door toevoeging van oxybutinine komt in* **hoofdstuk 7** *aan de orde.*
In **hoofdstuk 8** *wordt verslag gedaan van een retrospectieve studie naar de meest succesvolle techniek als chirurgie onvermijdelijk is geworden.*
Ten slotte gaat **hoofdstuk 9** *in op het belang van dieetadviezen aan CI-patiënten.*

Hoofdstuk 2

Ervan uitgaande dat elke CI-patiënt vroeg of laat bij een uroloog komt, wordt een enquête ontwikkeld en verstuurd naar alle urologen in Nederland. Van de formulieren komt 65% ingevuld terug.

Het aantal CI-patiënten per honderdduizend vrouwen boven de 18 jaar, wordt berekend op 8 à 16, wat overeen komt met uitkomsten van eerdere studies in Finland en Zweden. Een behoudende schatting, want alleen "actuele" CI-patiënten ("in dat jaar behandeld") worden geteld. Ter vergelijking de getallen voor gluten-overgevoeligheid (coeliakie): 15,9 per honderdduizend inwoners en multiple sclerosis: 65 per honderdduizend volwassenen. De CI-cijfers vallen nu des te meer op, de ziekte is immers nauwelijks bekend!

In de Verenigde Staten wordt het aantal CI-patiënten per honderdduizend volwassen vrouwen een factor 2 tot 10 hoger geschat. Een grotere alertheid en een andere diagnostiek verklaren mogelijk dit verschil. De afwijkingen in microscopisch onderzocht blaasweefsel worden door bijna 80% van de Nederlandse urologen aangeduid als een diagnostisch criterium bij CI, terwijl deze in de Verenigde Staten vrijwel geen rol spelen voor het stellen van de diagnose. Daarnaast heeft CI daar een veel grotere bekendheid onder artsen en patiënten door de actieve Amerikaanse CI-patiëntenvereniging.

De meeste CI-patiënten zijn vrouw; de mannen vormen nog geen 10%.

Opvallend is ook de uniformiteit onder Nederlandse urologen t.a.v. de behandeling. Ruim 80% kiest voor dimethylsulfaatoxide (DMSO) blaasspoelingen of de blaasdistensie volgens Helmstein als eerste of tweede therapie-optie.

Hoofdstuk 3

De diagnose CI wordt overwogen als andere aandoeningen uitgesloten zijn. Een diagnostische test bestaat er niet.

Ons onderzoek richt zich op het Tamm-Horsfall eiwit (THP). Dit wordt alléén in de nier geproduceerd en is het belangrijkste eiwit in de urine van gezonde individuen. Bij CI-patiënten wordt gemiddeld 69,8 milligram THP per 24 uur in de urine gemeten tegen 42,7 milligram gemiddeld bij 25 controle-patiënten. De controle-patiënten zijn vrouwen opgenomen met een urologische diagnose anders dan CI. Er is geen verschil in nierfunctie, leeftijd, gewicht, medicijngebruik of nevendiagnosen met de groep CI-patiënten. Het verschil in THP-uitscheiding in de urine blijkt statistisch significant en mag dus toegeschreven worden aan CI.

Vervolgens wordt bij 10 CI-patiënten onderzocht of de verhoogde THP-uitscheiding in de urine ook een neerslag van THP in het blaasweefsel veroorzaakt. Dit blijkt niet het geval.

De kans op het terecht uitsluiten dan wel aantonen van CI is op grond van de THP-uitscheiding resp. 67% en 78% (te laag om een betrouwbare diagnostische test te zijn). Deze verhoogde uitscheiding vanuit de nieren suggereert echter wel dat de oorzaak van CI niet alleen in de blaas gezocht moet worden.

Hoofdstuk 4

Een auto-immuun ziekte is eerder gesuggereerd als oorzaak van CI, met de blaas als specifiek "doel-orgaan". Er zijn dan ook enkele overeenkomsten tussen CI-patiënten en patiënten met auto-immuun aandoeningen:

- de geslachtsvoorkeur (meer dan 90% van de CI-patiënten is vrouw);
- de voorkeursleeftijd (meestal tussen de 30 en 60 jaar);
- de typische afwijkingen van het blaasweefsel bij microscopisch onderzoek: lymfocyten en niet zelden ook lymffollikels;
- het vaak sub-acute begin van de aandoening (dat jaren later nog gememoreerd wordt);
- het samengaan van CI met andere auto-immuun aandoeningen zoals SLE, M. Sjögren en reumatoïde arthritis.

In onze kliniek worden uit ingevroren serum van 22 CI-patiënten drie monsters willekeurig gekozen. Hieruit worden antilichamen geïsoleerd die in verschillende verdunningen op normaal en "ziek" blaasweefsel (van dezelfde CI-patiënt) worden gebracht. Met moderne technieken worden in alle drie de monsters specifieke auto-antilichamen tegen blaasweefsel, m.n. gericht tegen urotheel en spiervezels, aangetoond. De controles zijn negatief.

Daarnaast blijken twee van de drie onderzochte CI-patiënten anti-nucleaire antilichamen (ANA) in het serum te hebben. ANA gelden als aspecifiek kenmerk van auto-immuun ziekten.

De door ons gebruikte technieken werden niet eerder in relatie tot CI toegepast. De aanwezigheid van auto-antilichamen bij CI-patiënten versterkt de indruk dat een auto-immuun mechanisme een rol speelt bij het ontstaan van CI. Deze gedachte kan dienen als uitgangsstelling voor verder onderzoek naar het effect van immuunsuppressiva en corticosteroïden in de behandeling van CI.

Hoofdstuk 5

Het gebruik van pentosanpolysulfaat (PPS) als tablet voor de behandeling van CI werd eerder beschreven; over toediening rechtstreeks in de blaas werd niet eerder gepubliceerd.

Ons doel is de effectiviteit van PPS te verbeteren d.m.v. rechtstreekse toediening in de blaas. In een eerste oriënterend onderzoek krijgen zes CI-patiënten tweemaal per week PPS toegediend, met het verzoek dit zo lang mogelijk in de blaas te houden. De spoelingen worden uitstekend verdragen, zonder irritatie of bijwerking. Bij vier van de zes patiënten is sprake van een duidelijke verbetering en worden de spoelingen gedurende twaalf tot achttien maanden gecontinueerd.

Hoofdstuk 6

Gebaseerd op bovenstaande resultaten wordt een placebo-gecontroleerde studie ontworpen. Een groep van 20 CI-patiënten krijgt willekeurig PPS of placebo toegediend in de blaas, tweemaal per week gedurende drie maanden.

Verbetering kan worden aangetoond bij 40% van de patiënten in de PPS-groep tegen 20% in de placebogroep. Wat betreft de plas-frequentie en gemiddeld volume per plas zijn de verschillen voor en na behandeling, en PPS-groep vergeleken met placebo-

groep verwaarloosbaar. Bedacht moet worden dat het hier gaat om CI-patiënten bij wie eerder de gangbare behandelingen gefaald hebben. Belangrijker is dat 55% van de CI-patiënten uiteindelijk de PPS-blaasspoelingen continueert.

De praktische aspecten van de behandeling worden nu gestroomlijnd. Spoelingen worden in ®Urotainer-zakjes (minstens 6 weken houdbaar) aangeleverd, en alle patiënten leren het inbrengen van de blaasspoeling d.m.v. zelf-catheterisatie.

Hoofdstuk 7

Het effect van oxybutinine, toegevoegd aan de PPS-blaasspoelingen wordt in een vervolgstudie onderzocht.

Oxybutinine wordt al vele jaren als tablet of siroop voorgeschreven bij urologische klachten. Een beperkt aantal publikaties rapporteert over oxybutinine als blaasspoeling, voornamelijk kortdurend en bij patiënten met een "neurogene" blaas. In deze studies is de toename van de blaascapaciteit na toediening van oxybutinine in de blaas aanzienlijk. Bovendien blijken zich hierbij minder bijwerkingen voor te doen dan bij toediening van de bekende frequenties oxybutinine als tablet of siroop.

Deze gegevens vormen de basis voor onze studie naar het effect van oxybutinine gecombineerd met PPS.

In een studie bij 22 CI-patiënten wordt het effect van PPS-placebo blaasspoelingen vergeleken met PPS-oxybutinine spoelingen. De oplossing wordt driemaal per week in de blaas gebracht en de studie beslaat tweemaal zes weken.

De toevoeging van oxybutinine leidt inderdaad tot verhoging van het gemiddelde en maximale plas-volume en tegelijkertijd tot daling van de plas-frequentie vergeleken met PPS-placebo spoelingen.

Uiteindelijk continueren 14 CI-patiënten (70%) de PPS-oxybutinine spoelingen en 2 CI-patiënten de PPS spoelingen. Met deze gecontinueerde behandeling neemt het effect verder toe. Bovendien blijken het zelf-catheteriseren en zelf-mediceren voor de patiënten geen belemmeringen te zijn.

Hoofdstuk 8

De ernst en duur van de klachten en de na vele jaren vaak minimale blaascapaciteit maken chirurgie bij een aantal CI-patiënten onvermijdelijk. Een groot aantal chirurgische technieken is eerder toegepast bij CI waaronder blaasvergroting, blaasvervanging en een urine-stoma al of niet na het verwijderen van de blaas. Een bekende complicatie is terugkeer van de bekende pre-operatieve CI-symptomen.

Vaststelling van de meest effectieve chirurgische benadering is het doel van ons retrospectieve onderzoek.

Tussen 1976 en 1992 werden 27 CI-patiënten in het Academisch Ziekenhuis Groningen geopereerd, in totaal 45% van alle behandelde CI- patiënten in deze periode. Onderscheid wordt gemaakt tussen enerzijds blaasvergroting of -vervanging m.b.v. een darmsegment en anderzijds de operaties waarbij een (in)continent urine-stoma werd aangelegd.

Het verbreken van het contact tussen urine en blaas(rest) blijkt de essentiële factor voor het definitief verdwijnen van de CI-klachten. De consequentie hiervan is dat een totale verwijdering van de blaas bij CI-patiënten alleen aan de orde is als er vervolgens een volledige blaasvervanging met aansluiting op de plasbuis plaatsvindt.

Hoofdstuk 9

Dieetadviezen zijn een belangrijk onderdeel van de behandeling van en voorlichting over CI in de Verenigde Staten. Uit onze enquête blijkt dat 34% van de Nederlandse urologen soms dieetadviezen geeft aan CI-patiënten.

Om de waarde van deze dieetadviezen te onderzoeken worden de eetgewoonten van de CI-patiënt vergeleken met die van de gemiddelde Nederlander, aangepast naar geslacht en leeftijd. Van 16 CI-patiënten wordt een gedetailleerde dieet-anamnese afgenomen. Geen van deze patiënten heeft voorafgaande aan het interview dieet-informatie of -instructie gehad in relatie tot CI.

De CI-patiënten blijken minder calorieën en vet en meer vezels te consumeren. Een verklaring voor dit relatief gezonde dieet blijft speculatief. Mogelijk reflecteert het de intentie om, lijdend aan een chronische aandoening, als bestrijding van de kwaal gezonde voeding tot zich te nemen. Het kan ook anders zijn: chronische pijn en andere klachten kunnen de eetlust bederven.

Meer specifiek blijkt "slechts" 68% van de CI-patiënten koffie te gebruiken tegen 92% van de vergelijkbare gemiddelde Nederlandse bevolking. Daarentegen wordt thee, vooral allerlei soorten kruidenthee, door 100% van de CI-patiënten gebruikt. Bij alle andere "zure urine producerende" voedingsstoffen (o.a. sap van [citrus]vruchten) zijn geen verschillen aan te tonen.

Ten slotte. Moge dit proefschrift de (h)erkenning van cystitis interstitialis als chronische blaasaandoening ondersteunen en zo bijdragen aan een goede behandeling en voortgaand onderzoek.

APPENDIX A

VRAGENLIJST CYSTITIS INTERSTITIALIS

Bij de meeste vragen wordt een aantal elkaar uitsluitende antwoorden gegeven. Voor elk antwoord staat een cijfer. Wilt u steeds het antwoord dat aangeeft wat voor uw praktijk gebruikelijk is of overeenkomt met uw ervaring, **omcirkelen**. Graag bij deze vragen slechts één cijfer omcirkelen.

Bij een aantal vragen worden meerdere mogelijkheden genoemd waarbij voor elke mogelijkheid een 1 (= ja) en een 2 (= nee) staat. Wilt u in deze gevallen steeds **bij elke mogelijkheid** een 1 dan wel een 2 omcirkelen?

Bij twee vragen wordt een opsomming gegeven (van symptomen respectievelijk therapieën). Hierbij wordt u gevraagd een keuze te maken en een **rangorde** aan te geven door achter de cijfers 1, 2 en 3 uw keuze in te vullen. Hierbij kunt u volstaan met de letters waarmee de genoemde symptomen/therapieën zijn aangegeven.

Indien u geen patiënten met cystitis interstitialis of soortgelijke klachten onder behandeling heeft, wilt u dan het eerste antwoord bij vraag 1 en vraag 2 (te weten **0 patiënten)** omcirkelen en het formulier **wel** terug sturen?

Het zal u ongeveer 10 minuten kosten om de vragen te lezen en de antwoorden te omcirkelen. Onze dank voor uw medewerking.

1. Hoeveel (nieuwe en oude) patiënten met **niet-bacteriële cystitis klachten (painful bladder, sensorische/mot. urge, cystitis interstitialis, urethraal syndroom, prostatodynie met dysurische klachten)** komen op jaarbasis op uw spreekuur?

   1 0
   2 1 - 10
   3 10 - 50
   4 50 - 100
   5 100 - 200
   6 meer dan 200, namelijk .....

2. Hoeveel (nieuwe en oude) patiënten uit deze groep blijken cystitis interstitialis te hebben, op jaarbasis?

1 0
2 1 - 5
3 5 - 10
4 10 - 15
5 15 - 20
6 meer dan 20, namelijk .....

3. In welke leeftijdsgroep ziet u cystitis interstitialis het meest?

1 jonger dan 20 jaar
2 20 - 40 jaar
3 40 - 60 jaar
4 ouder dan 60 jaar

4. Komt de diagnose cystitis interstitialis naar uw ervaring ook bij mannen voor?

1 ja
2 nee

<u>Zo ja:</u> wat is naar uw ervaring de verhouding man : vrouw?

1 1 : 2
2 1 : 5
3 1 : 10
4 anders, namelijk .... : ....

5. Hoe lang is de gemiddelde ziektegeschiedenis van uw patiënten met cystitis interstitialis?

1 1 - 2 jaar
2 3 - 5 jaar
3 meer dan 5 jaar, namelijk .... jaar

6. Er is geen eenduidige mening omtrent de oorzaak van cystitis interstitialis. Een aantal oorzaken wordt genoemd in de literatuur. Wat is in uw opinie de meest waarschijnlijke oorzaak van cystitis interstitialis? **(S.v.p. één cijfer omcirkelen.)**

1 onbekend
2 neurogeen
3 immunologisch (auto-imuunziekte)
4 urothele dysfunctie (verhoogde permeabiliteit)
5 psycho-somatisch
6 infectieus (viraal, ander micro-organisme)
7 anders, namelijk .....

7. Bij hoeveel procent van **uw** patiënten met cystitis interstitialis vindt **u** dat er ook een duidelijke psychosomatische component is?

1 0%
2 < 25%
3 25 - 50%
4 50 - 75%
5 75 - 100%

8. In de literatuur wordt een aantal meer of minder typische symptomen in de anamnese bij patiënten met cystitis interstitialis beschreven. Deze staan hieronder vermeld. (Een mogelijk niet genoemd symptoom dat u wel als typisch voor cystitis interstitialis beschouwt, kan bij H ingevuld worden.)

A) pollakisurie, een mictiefrequentie die variëert van 10-40 keer per dag
B) pijn suprapubisch, in het kruis of in de rug
C) het typische aspect dat blaaslediging de pijnklachten verlicht
D) 'urge' gevoelens, het gevoel "de hele dag wel te kunnen plassen"
E) nycturie, meer dan 4 maal
F) een ziektegeschiedenis die minimaal één jaar lang is
G) een familie-anamnese met cystitis interstitialis, reuma, M. Crohn of S.L.E.
H) anders, namelijk .....
.....

Wilt u hieronder aangeven welke van deze klachten **u** als **typisch** voor cystitis interstitialis beschouwt. Wilt u de drie belangrijkste klachten invullen achter 1, 2 en 3. Graag een rangorde aanbrengen, dit wil zeggen de meest typische klacht bij 1, etc. (U kunt volstaan met het invullen van de bijhorende letter.)

1) .....
2) .....
3) .....

9. Op het moment dat **u** een patiënt op uw spreekuur verdenkt van cystitis interstitialis, welke aanvullende diagnostiek zult u dan inzetten om meer zekerheid omtrent de diagnose te krijgen? S.v.p. **bij elke mogelijkheid** 1 (= ja) dan wel 2 (= nee) omcirkelen.

Ja	**Nee**		
1	2	A)	urinekweek
1	2	B)	urinecytologie
1	2	C)	echo nieren
1	2	D)	I.V.P.
1	2	E)	cystoscopie
1	2	F)	blaasbiopten met behulp van loc. anaesth.
1	2	G)	cystoscopie en/of biopten onder anaesthesie
1	2	H)	flowmetrie
1	2	I)	echo prostaat
1	2	J)	uro-dynamisch onderzoek
1	2	K)	anders, namelijk .....

Vraag 10 alleen beantwoorden als u **uro-dynamisch onderzoek** uitvoert.

10. Hieronder zijn een aantal uro-dynamische bevindingen gerangschikt, waarvan sommige de diagnose cystitis interstitialis ondersteunen, andere deze juist uitsluiten. Wilt u aangeven welke informatie **u** wilt hebben als u een U.D.O. doet bij een patiënt verdacht voor cystitis interstitialis.

Ja	**Nee**		
1	2	A)	compliance, een slechte compliance zou passen bij cystitis interstitialis
1	2	B)	detrusor instabiliteit, in principe een exclusie-criterium voor de diagnose cystitis interstitialis
1	2	C)	blaascapaciteit, sommigen claimen dat deze bij een cystitis interstitialis kleiner dan 400 cc. moet zijn
1	2	D)	urethra instabiliteit, een instabiele urethra kan een apart syndroom zijn
1	2	E)	obstructieve mictie, dyssynergie is verdacht voor een neurogene blaas
1	2	F)	'first desire', bij klein volume suggestief voor sens. urge en/of cystitis interstitialis
1	2	G)	pijn bij blaasvulling met klein volume, dit past bij cystitis interstitialis
1	2	H)	residu na mictie, dit suggereert andere aandoeningen
1	2	I)	anders, namelijk ....

11. Welke van de volgende criteria gebruikt u om de diagnose cystitis interstitialis te stellen?

Ja	**Nee**		
1	2	A)	typische anamnese al of niet in combinatie met mictielijst
1	2	B)	U.D.O.
1	2	C)	cystoscopische bevindingen
1	2	D)	cystoscopische bevindingen in narcose
1	2	E)	P.A. blaasbiopten
1	2	F)	de aanwezigheid van mestcellen in de P.A. van blaasbiopten
1	2	G)	de diagnostische criteria opgesteld door de Nat. Health Institutes of the U.S.A.[1]
1	2	H)	anders, namelijk ....

12. Wat is uw **primaire** keus van behandeling? Wilt u **alleen** het cijfer omcirkelen van de behandeling waarmee u **primair start** als u de diagnose cystitis interstitialis gesteld heeft. Anticholinergica en anti-biotica zijn niet genoemd omdat deze bijna altijd al in vele vormen zijn geprobeerd. Mocht u toch primair met zo'n middel starten, wilt u dat dan achter **L** invullen?

1	A)	Amitryptiline (Tryptizol) oraal
2	B)	pentosan-polysulfaat (Elmiron) oraal
3	C)	corticosteroïden locaal en/of systemisch (oraal)
4	D)	DMSO blaasspoelingen
5	E)	zilver-nitraat blaasspoelingen
6	F)	catheter à demeure
7	G)	hydrodistensie volgens Helmstein
8	H)	submucosale anti-flogistische injecties
9	I)	blaas-augmentatie
10	J)	urinedeviatie zonder cystectomie
11	K)	urinedeviatie met cystectomie
12	L)	anders, namelijk .....

[1] De criteria zijn gepubliceerd in de J. of Urology 1988; Vol. 140: 203-206.

13. Indien uw primaire therapie onvoldoende resultaat geeft, kunt u dan aangeven welke uw **volgende therapie-opties** zijn, en in welke volgorde u deze doorgaans toepast? Wilt u hiervoor de antwoordmogelijkheden A t/m L van vraag 12 gebruiken en de bijhorende letter achter 1, 2 en 3 invullen. Graag een rangorde aanbrengen, dit wil zeggen uw eerste optie bij 1, uw tweede bij 2, etc.

    Mijn volgende therapiestappen zullen zijn:

    1) .....
    2) .....
    3) .....

14. Bij welk percentage van **uw** patiënten met cystitis interstitialis vindt er uiteindelijk chirurgische therapie plaats?

    1 nooit
    2 < 5%
    3 5 - 25%
    4 25 - 50%
    5 50 - 75%
    6 > 75%
    7 altijd

15. Welke chirurgische therapie heeft uw voorkeur?

    1 cystectomie craniaal van de int. sfincter met blaasvervanging
    2 augmentatie cystoplastiek
    3 totale cystectomie met urinedeviatie
    4 cystolysis
    5 anders, namelijk .....

16. Met name in Amerika worden ook uitgebreide dieetadviezen gegeven, zoals het vermijden van alcohol, citrusvruchten en -dranken, onthouding van caffeïne zoals in koffie, thee en chocola. Geeft u zelf ook dieetadviezen?

    1 ja
    2 nee

17. Hoe denkt u over de volgende stelling:

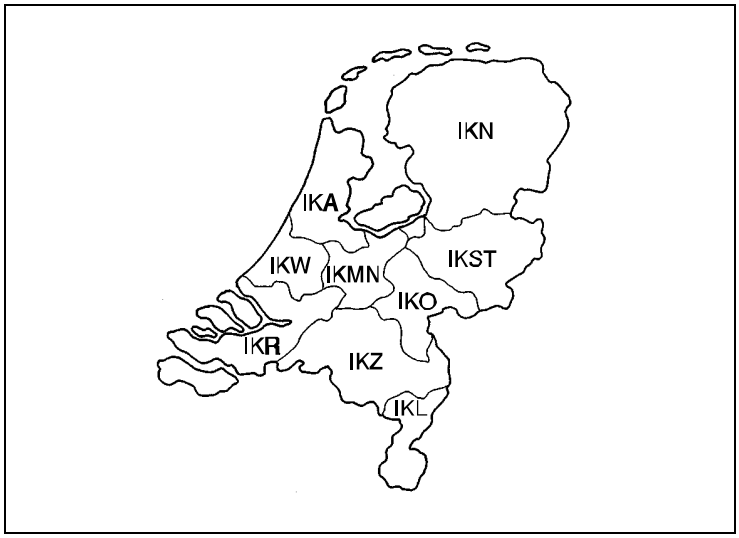
    "Patiënten met prostatodynie en urge/pollakisurie klachten hebben mogelijk cystitis interstitialis; het doen van een cystoscopie verdient sterke aanbeveling bij deze patienten".

    1 eens
    2 oneens

18. Wilt u een schatting maken van het aantal patiënten waarbij **u** in 1992 de diagnose prostaat- of blaaskanker stelde. Het gaat dus om **uw individuele schatting**, niet het cijfer van de hele maatschap indien u met meerdere urologen in een ziekenhuis werkt. Met blaaskanker bedoelen wij de invasieve tumoren: T1 t/m T4, **niet** Ta of CIS. Door deze schattingen te vergelijken met de gegevens van de 9 regionale Integrale Kanker Centra hopen wij vergelijkenderwijs ook een uitspraak over de betrouwbaarheid en geografische spreiding van de c.i.-schattingen te kunnen doen.

    Schatting van uw aantal **nieuwe** blaaskankerpatiënten (T1 t/m T4)
    in 1992: .....

    Schatting van uw aantal **nieuwe** prostaatkankerpatiënten
    in 1992: .....



Uw ziekenhuis valt in de volgende regio (zie kaartje), s.v.p. omcirkelen:

1	IKN	Noord-Nederland
2	IKA	Amsterdam
3	IKST	Stedendriehoek Twente
4	IKO	Oost
5	IKMN	Midden Nederland
6	IKW	West
7	IKR	Rotterdam
8	IKZ	Zuid
9	IKL	Limburg

Onze hartelijke dank voor uw medewerking. Uiteraard zult u over enige tijd de resultaten van deze enquête te zien krijgen.

CHAPTER13

Patienteninformatie: Brochure AZG-Groningen.

BLAASPIJNSYNDROOM

cystitis interstitialis

AFDELING CHIRURGIE/UROLOGIE

INLEIDING

U krijgt deze brochure omdat uw behandelend dokter denkt dat het **blaaspijnsyndroom** (Cystitis Interstitialis in het medisch taalgebruik) de oorzaak van uw klachten is.
Deze brochure is gemaakt om u en uw huisarts antwoord te geven op mogelijke vragen. De aandoening is niet eens zo zeldzaam, maar wel heel onbekend. Daarom willen wij deze brochure gebruiken om uit te leggen dat u niet de enige bent met deze klachten, wat er eigenlijk aan de hand is met uw blaas, wat u zelf er aan kunt doen en wat uw dokter er aan kan doen. Het laatste gedeelte is vooral voor uw huisarts bestemd en bevat dus meer medische termen.
Omdat cystitis interstitialis de meest gebruikte benaming is, zowel nationaal als internationaal kiezen wij voor deze naam.

HOE BEGINT CYSTITIS INTERSTITIALIS (BLAASPIJNSYNDROOM)

Cystitis interstitialis begint vaak als een blaasontsteking met pijn onder in de buik of in het kruis, frequente aandrang en vaak plassen. Soms komt de ’blaasontsteking’ zo maar uit de lucht vallen, soms begint het na een operatie, vooral operaties aan de baarmoeder worden nog al eens genoemd.
Antibioticakuren blijken weinig of niet te helpen, de klachten gaan niet over, integendeel ze worden langzaam maar zeker erger. Meestal is het een stekende pijn onder in de buik, vaak ook stekend in de schede. Dit kan ook het vrijen heel pijnlijk, zo niet onmogelijk maken. Soms trekt de pijn naar de liezen of rug. Dan begint ook op te vallen dat plassen de pijn verlicht, een opgelucht gevoel geeft. Er is een duidelijke relatie tussen pijn en vaak plassen. Als ook ’s nachts het plassen met steeds kortere tussenpozen moet gebeuren ontstaat oververmoeidheid, wanhoop en vloeien er tranen. Reizen en bezoekjes zijn nauwelijks meer mogelijk, winkelen wordt beheerst door de vraag ’waar is het volgende toilet’? Soms doet de patiënte in wanhoop een luier om, ’dan loopt het maar weg’. Of er staat een emmertje in de auto, zodat niet telkens gestopt hoeft te worden.
Van pijn kun je zo niet gek, dan zeker wel wanhopig worden. Zeker als de diagnose niet gesteld wordt. Sommigen patiënten komen zelfs bij een psychiater terecht. Daarom is een juiste diagnose zo belangrijk, dan weet u en uw omgeving dat de hoofdoorzaak van alle klachten ’beneden’ in de blaas zit, en niet ’boven’ tussen de oren.

WAT IS CYSTITIS INTERSTITIALIS (BLAASPIJNSYNDROOM)

De blaas is een orgaan wat helemaal onder in het bekken ligt, bij de vrouw tussen baarmoeder en schaambeen, bij de man tussen endeldarm en schaambeen. De blaas dient als opslagruimte voor urine en als uitdrijforgaan voor urine. Normaal gebeurt dit tussen de 4 en 8 keer op een dag.
Bij cystitis interstitialis is sprake van een ernstige ontsteking van het blaasslijmvlies. Het lijkt wel wat op een 'gewone' blaasontsteking, in het geval van cystitis interstitialis is er echter **geen** bacterie als oorzaak. Daarom helpen antibiotica ook niet of kortdurend. De eigenlijke oorzaak is onbekend. Misschien is het lichaam's eigen afweersysteem ziek, en wordt zodoende eigen blaasweefsel "aangevallen". Misschien is er iets mis met de beschermende slijmlaag van de blaaswand, waardoor allerlei stoffen in de urine de blaaswand veel meer irriteren dan normaal. Kortom de precieze oorzaak en het werkingsmechanisme zijn niet bekend. Maar u zit met de klachten, en daar moet wat aan gebeuren.

BELANGRIJK

Ook al weten we niet wat de oorzaak is, we weten wel dat het **geen kanker** is. Cystitis Interstitialis is een goedaardige aandoening, waar mensen **niet** aan dood gaan, maar die wel zeer hardnekkig en heel langdurig kan zijn. Soms wordt de toestand zo onhoudbaar, dat patiënt en dokter besluiten dat de blaas operatief verwijderd moet worden. Zo iemand krijgt dan een urine stoma.

HET STELLEN VAN DE DIAGNOSE

Voor dat er iets kan gedaan worden, moet eerst de diagnose met zekerheid gesteld worden. Bijna altijd komt iemand met verdenking op cystitis interstitialis bij een uroloog terecht. Een **uroloog** is een chirurgisch specialist van nieren, urinewegen, blaas en geslachtsorganen. Om de diagnose te kunnen stellen zal er onderzoek moeten gebeuren, en zullen ander ziekten die soortgelijke klachten kunnen geven uitgesloten moeten worden. Behalve lichamelijk onderzoek wordt er meestal ook urine en bloed onderzocht. Vaak zal gevraagd worden een zogenaamde plaslijst bij te houden, waarop u 24 uur lang noteert wanneer en hoeveel u plast. Vervolgens wordt er in de blaas gekeken, een *cystoscopie* heet dat. Dat kan heel goed poliklinisch met plaatselijke verdoving, maar wordt ook vaak tijdens een korte opname gedaan om gelijktijdig kleine stukjes weefsel (*biopten*) uit de blaas te nemen voor microscopisch onderzoek.
Een zogenaamd *uro-dynamisch onderzoek* gebeurt ook vaak. Bij dit onderzoek wordt een dun

slangetje via de plasbuis in de blaas gebracht, waarbij de blaas met warm water wordt gevuld, en dus eigenlijk het normale plassen wordt nagebootst. Door druk- en volumemeting kan de dokter dan vaststellen, hoeveel vocht uw blaas kan bevatten, wanneer uw aandrang en wanneer u pijn voelt, en of er ook blaaskrampen zijn. Pas als een aantal bevindingen positief zijn en een aantal andere oorzaken uitgesloten zijn, kan de diagnose cystitis interstitialis gesteld worden.

HOEVEEL MENSEN MET CYSTITIS INTERSTITIALIS ZIJN ER ?

Cystitis Interstitialis is eigenlijk al heel lang bekend als ziektebeeld. Een zekere dokter hunner (chirurg) beschreef het beeld al in 1914, in Amerika. Maar eigenlijk komt het in de hele wereld voor, alleen is over het aantal mensen dat er door getroffen is, nog steeds weinig bekend. In 1994 is door het Academisch Ziekenhuis Groningen een enquête onder urologen gehouden over cystitis interstitialis. Onder mannen komt de aandoening nauwelijks voor, de vrouw/man verhouding is 10 : 1, d.w.z. dat vrouwen 10 maal zo vaak door cystitis interstitialis worden getroffen dan mannen. Per 100.000 vrouwen zijn er 6 tot 18 cystitis interstitialis patiënten, dit betekent dat er in Nederland een groep van **500 tot 1500** cystitis interstitialis patiënten is. Dat zijn dan patiënten die daadwerkelijk klachten hebben en behandeld worden door een uroloog. Waarschijnlijk is de groep die ooit behandeld is maar waar nu sprake van een acceptabele situatie is, of die een stoma heeft gekregen, nog eens zo groot.

WAT KAN ER AAN GEDAAN WORDEN ?

Er is een schier eindeloze lijst van medicijnen geprobeerd. Soms werkt zo'n medicijn wel, maar vaak is onduidelijk of de werking van het medicijn niet toevallig samen valt met een spontane verbetering van de klachten.

Naast medicijnen die als tablet of capsule doorgeslikt moeten worden, wordt soms ook gebruik gemaakt van medicijnen die in de blaas zelf gebracht worden, d.m.v. een catheter, een zogenaamde blaasspoeling. Een bekende blaasspoeling is de D.M.S.O. blaasspoeling, deze wordt eens in de 4 a 6 weken in de blaas gebracht. In het Academisch Ziekenhuis Groningen wordt momenteel onderzoek gedaan naar het effect van blaasspoelingen met Pentosan-polysulfaat. Het voordeel van blaasspoelingen is dat het medicijn in hoge concentratie op de plaats van de klachten gebracht wordt. Daarnaast is belangrijk dat het geur- en kleurloze Pentosan geen bijwerkingen heeft. Maar ongetwijfeld zal ook Pentosan niet het gehoopte 'wondermiddel' zijn.

Een reeds lang bekende behandeling is het zogenaamde oprekken van de blaas. De Duitse arts Helmstein, heeft deze methode in de jaren ’70 ontwikkeld. Na verdoving d.m.v. een prik in de rug wordt een catheter met condoom in de blaas gebracht, waarna deze onder druk gedurende 1 tot 6 uren gevuld wordt. Na dit oprekken is een groot aantal patiënten enige maanden klachtenvrij. Helaas blijkt ook deze behandeling vrijwel nooit afdoende te zijn.

Zolang er geen genezend medicijn bestaat, blijft de begeleiding van een cystitis interstitialis patiënt het belangrijkste aspect van de behandeling. Samen blijven zoeken naar middelen en mogelijkheden om verlichting te brengen en een acceptabele situatie te creëren. Uroloog en huisarts kunnen hier een belangrijke rol in spelen.
Voor een cystitis interstitialis patiënt is het vaak een hele opluchting om even ’het hart te kunnen luchten’, of te horen dat de oorsprong van de klachten onder in de buik zit en niet ’tussen de oren’.
Samen kunnen patiënt en arts naar verlichting van de klachten zoeken. Het staat er zo mooi, maar in de praktijk blijkt nogal eens dat het leed van de patiënt en de machteloosheid van de arts op gespannen voet met elkaar staan.

Alleen in het uiterste geval moet overgegaan worden tot een operatie.

WAT KUNT U ZELF DOEN ?

Veel kunt u zelf doen ! Leer uw eigen lichaam kennen, probeer uit te vinden wat de klachten verergert, en waarmee het juist beter gaat. En bedenk, dat er altijd spontane verbeteringen, maar helaas ook spontane verslechteringen zijn. Vaak raakt de aandoening na een aantal (3 tot 10 jaar) als het ware "uitgeblust", de pijn verminderd, wordt ’draagbaar’ en de frequentie van plassen wordt ’acceptabel’.

DIEET

Het dieet **kan** een rol spelen, maar hoeft niet. Sommige patiënten vinden verlichting door citrus-vruchten te vermijden. Ook van koffie, alcohol, chocola en gekruid eten wordt gezegd dat dezen de klachten kunnen doen verergeren. Het beste kunt u dit voor u zelf vaststellen door een periode van 3 weken iets niet te gebruiken. Noteer hoe vaak u in 24 uur naar de WC bent geweest en hoeveel pijnstillers u heeft geslikt. Laat vervolgens bijv de koffie een aantal weken staan, noteer nogmaals en vergelijk.
Uit onderzoek in het Academisch Ziekenhuis Groningen naar het dieet van cystitis interstitialis patiënten is geen positieve of negatieve invloed van bepaalde voedingsstoffen vastgesteld. Veel of

weinig drinken moet ieder voor zich bepalen. Er is **geen** reden om veel te drinken.

WARMTE

Kou (winter) heeft vaak een slechte invloed op de klachten, warmte daarentegen vaak een goede. Probeer daarom warme kleding te dragen, en warm ondergoed. Een elektrisch deken of een warme kruik kunnen ’s nachts aangenaam zijn. Een warm, heel warm zitbad gedurende 20 tot 30 minuten geeft vaak verlichting van de pijn. Als er geen ligbad is, kan een babybadje gebruikt worden.

SEX

Soms is sexuele gemeenschap niet meer mogelijk doordat de plasbuis en de blaas te pijnlijk zijn. Natuurlijk zijn vrijen en sex meer dan alleen een coïtus. Maar toch. Daarom is
er over praten met de partner, samen naar andere oplossingen zoeken heel belangrijk. Een langdurig zitbad van te voren, eventueel gecombineerd met een pijnstiller of zetpil kan vaak goed helpen.

STRESS

Stress heeft een slechte invloed. Stress vermijden is makkelijker gezegd dan gedaan. De chronische pijn op zich is al een oorzaak van stress. Daarom is afleiding, een hobby of een sport heel belangrijk. Soms kunnen yoga oefeningen goed helpen.

Chapter 14

Dankwoord

Een promotie-onderzoek lijkt wel eens *één voor zichzelf en allen voor één*. Het was daarom bijzonder en inspirerend dat telkens mensen mijn verhaal wilden aanhoren en geïnteresseerd raakten, dat ik steeds met vragen en suggesties verder geholpen werd. Velen hadden een actief aandeel in de realisatie en uitwerking van de verschillende onderzoeken. Sommigen wil ik persoonlijk noemen.

Bij de eerste *(niet gepubliceerde)* 'pilot-studie' met blaasspoelingen kregen cystitis interstitialis (CI)-patiënten tweemaal per week een blaasspoeling met ®Adalat in het ziekenhuis. De opvang van CI-patiënten, het bestellen, bewaren en toedienen van de spoelingen was alleen mogelijk door de inzet van Ineke Hofman, Lineke Kroon, Yolanda Manduapessy, Rika Pool, Dorothé Raatjes, Chientje Vos en Mirjam Zwiep, de verpleegkundigen op het functiecentrum chirurgie-urologie. Later leerden patiënten zelf-catheterisatie en namen zij de spoelingen mee naar huis. Vaak gebeurde dit tijdens een kortdurende opname. De vele verpleegkundigen van wat toen B2VA was en nu B4VA is, ben ik erkentelijk voor hun inzet en vooral betrokkenheid. Jantje Boer, secretaresse van de afdeling urologie, was daarbij een vast herkenningspunt en onmisbare administratieve schakel. Bert de Ruiter, collega uroloog en organisator in hart en nieren, was steeds bereid om het proces verder te stroomlijnen.

Op de 13e etage van het gebouw voor gynaecologie en verloskunde zetelt de sectie epidemiologie. Het waren de scherpe vragen van Bert Rijcken die de basis vormden voor een gedegen enquête. Dank zij het sorteerwerk op de postkamer van Annet Dijkstra en Marijke Reitsma viel de enquête inderdaad op zaterdag door de bus bij alle Nederlandse urologen. De volgende maandag waren er al 55 retour. Al het invoeren, verwerken en berekenen werd door Anita de Graaf gedaan. Zij was telkens bereid nieuwe vragen aan te horen en gewijzigde uitdraaien te maken.

In Jan Marrink trof ik een geïnteresseerd, ter zake kundig klinisch chemicus, die meedacht en de ELISA- essays opzette. Harry Klip deed de letterlijk honderden Tamm-Horsfall bepalingen.
Er is geen onderzoek of de patholoog komt eraan te pas. Dank zij de inspanningen van Arend Karrenbeld kwamen de speciale kleuringen en vriescoupes er. De vriescoupes waren nodig voor het onderzoek naar antilichamen, uitgevoerd door Anita ter Haar op het immunologisch laboratorium onder leiding van mijn tweede promotor Lou de Leij. Op de kamer van Lou de Leij, een stukje oude AZG glorie, werden de auto-imuun hypothesen doorgenomen (soms onder de rook van een sigaar) wat uiteindelijk zijn vruchten afwierp.

Met enige regelmaat ging een van mijn voettochten, het AZG is een groot complex, naar de apotheek. Door de ervaring en nuchterheid van Marianne Laseur konden mijn

ideeën ook studies worden. Barbara Laurens heeft dat geweten, een dramatische stijging in de produktie van steriele blaasspoelingen was het gevolg.

Jenny Peeters deed een gedetailleerde dieetanamnese bij 16 CI-patiënten. Bij het verwerken van de resultaten en het laten rijpen van de conclusies was haar prettige vasthoudendheid een belangrijke hulp.
Roelie Dagelet werd van secretaresse redactrice bij de uitstroom van tabellen, artikelen en dia's. Haar enthousiasme en streven naar perfectie heeft menig blunder voorkomen.

De inzet van mijn eerste promotor Han Mensink heeft als een rode draad door het onderzoek gelopen. Ik kreeg binnen een drukke kliniek ruimte om onderzoek te doen naar een vrijwel onbekende (en daardoor vaak onbeminde) blaasaandoening. Er ontstond zelfs een speciale CI-polikliniek. En ondanks alle taken en zorgen van een professor stond de deur van zijn kamer altijd open om even te overleggen, iets te bespreken of gewoon te kletsen na zessen.

De steun van velen is hierboven gememoreerd. Op sommige momenten is er net iets meer nodig om het werkelijk een proefschrift te laten worden. Die "push" kreeg ik thuis. Ik denk bij voorbeeld aan het moment dat ik mijn eerste "Amerikaanse" voordracht proefdraaide voor Ischa, Jefta, Janelle en Ella. Op cruciale momenten was het El die zei: "En nu moet je doorpakken."

Zonder het correctiewerk van Judith Abma, de stimulerende hulp van mijn vriend en neerlandicus Johannes de Geus en de lay-out van mijn broer Herman had het niet kunnen worden wat het nu is. Betty Notenboom is gezegend met een arends-blik, zij deed het finale correctiewerk.

Ten slotte. Ik wil ieder die (in)direct bij dit onderzoek betrokken was, hartelijk danken. Zo is het geworden een onderzoek dóór mensen en naar ik vurig hoop ook een onderzoek vóór mensen.

Chapter 15

Curriculum vitae

Jurjen Jacob Bade

June 9, 1956	Firstborn of Jaap Bade and Nel Kuijvenhoven. Eldest of five brothers. Married to Ella van de Kraats. Together we have three children: Ischa, Jefta and Janelle.
1968-1974	VWO, Peter Stuyvesant college - Curaçao and Corderius college - Amersfoort.
1974-1981	M.D. grade at the Medical Faculty of Utrecht.
1981-1983	Surgical and Obstretical training, Salem Hospital - Ermelo
1983-1988	Medical Officer Nyanje R.C.Z. Hospital, Zambia
1988-1991	Resident in training, general surgery, Deventer Hospital - Deventer - Head: Dr. P. van Elk
1991-1992	Resident in training, urology, Deventer Hospital - Deventer Head: Y.G.V.M. Ypma
1992-1995	Resident in training, urology, University Hospital Groningen - Groningen Head: Prof. dr. H.J.A. Mensink
1995-1996	Urologist, University Hospital Groningen - Groningen
Juli 1, 1996	Urologist, St Anna Hospital Oss and G.Z.G. Hospital 's-Hertogenbosch